ALPORT'S SYNDROME OF HEREDITARY NEPHRITIS WITH DEAFNESS*

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THE first report of an apparent familial inheritance of renal disease was made by Dickinson in 1875. He referred to three generations of an ancient family in which 11 out of 17 members had albuminuria, and several died prematurely of Bright's disease. He also remarked that the complexions in the family portraits dating back to the Wars of the Roses had a clear transparent pallor suggestive of renal disease. During the subsequent fifty years several workers reported familial nephritis.

In some families (Kidd 1882, Pel 1899, Aitken 1909) there appears to have been a true hereditary trait extending over two or more generations; but in others (Attlee 1901, Eason and Smith 1924) the disease affected several members of a family more or less simultaneously and cannot therefore be regarded as hereditary. Of particular interest is a family first mentioned by Guthrie in 1902. Further cases from the same family were added by Kendall and Hertz in 1912 and by Hurst in 1923. The final report about this family was made by Alport in 1927. In this final version he refers to 29 members over four generations (fig. 1). Of these, 7 males and 7 females showed evidence of nephritis; 5 of the males had died before they were 20 years old, while the oldest affected male survivor was only 13. Of the females, however, only 1 had died prematurely. Alport also commented on the fact that 11 members (7 females and 4 males) had also a perceptive type of deafness. He pointed out that, whereas the male members of the family were most severely affected, the disorder appeared to be transmitted by the females.

For nearly twenty-five years there were no further reports of this syndrome; but in 1951 Perkoff et al, published a preliminary account of a large Mormon family with an apparently similar disorder. In the past ten years reports concerning some nineteen more families with over 250 affected individuals have appeared. These have come from the U.S.A. (Reyersbach and Butler 1954, Sturtz and Burke 1956, Robin et al. 1957, Castleman 1957, Klotz 1959, Russell and Smith 1959, Chappell and Kelsey 1960), Canada (Goldbloom et al. 1957), France (Hamburger et al. 1956, Morin et al. 1958), Germany (Nieth 1959, Fuhrman 1959), Italy (Poli 1953), and Israel (Sohar 1956); but none has come from Great Britain. The observations by these workers have to some extent amplified those in Alport's original paper, and the main features of the syndrome can now be summarised as following:

Inheritance

By careful study of some large family trees the nature of the genetic linkage has been determined. According to Perkoff et al. (1958) the renal lesion is transmitted as a partially sex-linked dominant trait, and most other workers seem to agree with this view. There is less agreement on the mode of inheritance of the deafness. According to Hamburger et al. (1956) it is by a partially sex-linked recessive gene, but Perkoff et al. suggest that it is linked with the renal lesion in some as yet unknown way.

The Renal Disorder

The clinical presentation of the renal disorder seems to vary somewhat between different families. In most, symptomless hæmaturia and albuminuria have been the first findings, and when specifically sought these have been found in the first week or so of life (Morin et al. 1958). In this early phase renal-function tests and an occasional renal biopsy have been found to be normal. In the majority of affected males, however, the disorder proceeds insidiously to chronic nephritis from which they die, usually before reaching the age of 30, and sometimes much earlier. The females, on the other hand, are seldom severely affected, and most seem to have a normal expectation of life despite recurrent or continuous albuminuria. In these families the kidneys of those members who have died of renal failure show the usual histological changes of chronic glomerular nephritis. There may be severe interstitial lymphocytic infiltration, and in some cases large numbers of lipid-containing foam cells have been seen (Goldbloom et al. 1957, Perkoff et al. 1958, Castleman 1957). Some workers have suggested that the renal disorder may be a recurrent pyelonephritis (Goldbloom et al. 1957, Perkoff et al. 1958), but the evidence they put forward is not very convincing. Robin et al. (1957) believe that there may in fact be two different but related syndromes—one due to a form of glomerular nephritis, which is transmitted as a partially sex-linked dominant trait, and the other due to pyelonephritis, transmitted as a simple dominant. Possibly the family recently reported by Løken et al. (1961) from Norway may come into the second group.

The Auditory Disorder

In all cases the deafness has been found to be of the perceptive type. This usually comes on gradually, being first noticed at about the age of 10, and it may later become very disabling. It has been reported in the majority of affected males but in a considerably smaller proportion of the females. Occasionally, deafness has been reported in individuals without apparent renal involvement. No satisfactory reports of the histological appearances of the inner ear in this disorder are available.

Ophthalmic Defects

Several observers have also commented on the occurrence of various congenital occular defects in their patients. Particular mention has been made of cataracts and of spherophakia (Sohar 1956).

Reports of this syndrome have appeared under different descriptive titles which are often rather

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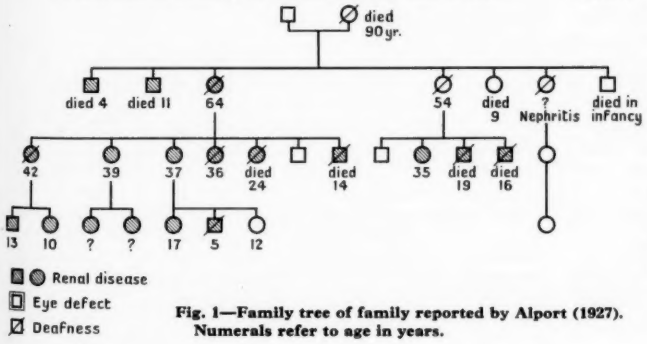

Fig. 1—Family tree of family reported by Alport (1927). Numerals refer to age in years.

cumbersome and, since the ætiology is still unknown, may well be inaccurate. It seems therefore that a case can be made for the use of an eponymous title, at least for the time being. If this is accepted, then Alport's name is the obvious choice since it was he who first described the main features of the syndrome. I suggest therefore that the syndrome should in future be referred to as " Alport's syndrome ".

I describe here the findings in three affected families.

Findings

FAMILY A (FIG. 2)

A boy, aged 13 (case 1), presented at the age of $2^1/_2$ years with hæmaturia, slight œdema, and oliguria. The œdema and oliguria quickly subsided, but the hæmaturia persisted despite prolonged rest in hospital and after his return home. At the age of 4 years he was admitted to Guy's Hospital under Dr. Philip Evans. Investigations all gave negative results. An attempt to control the hæmaturia with cortisone proved unsuccessful, and it was established that the amount of activity permitted made no difference to the Addis count. During the subsequent nine years the patient has developed normally, but his hæmaturia has persisted. Every specimen of his urine that has been tested has contained numerous red blood-cells, and he has continued to have frank hæmaturia with each minor infection. A little protein is present in the urine, but casts have seldom been observed. There is still no

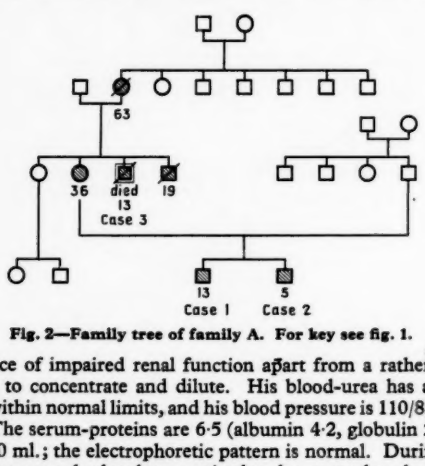

Fig. 2—Family tree of family A. For key see fig. 1.

evidence of impaired renal function apart from a rather poor ability to concentrate and dilute. His blood-urea has always been within normal limits, and his blood pressure is 110/88 mm. Hg. The serum-proteins are 6·5 (albumin 4·2, globulin 2·3) g. per 100 ml.; the electrophoretic pattern is normal. During the past two years he has been noticed to be somewhat deaf, and on testing he was found to have a loss of up to 35 decibels in the higher frequencies in both ears.

Case 2, aged $5^1/_2$ years, the brother of case 1, first attended hospital at the age of 12 months with a history of intermittent mild hæmaturia. Red blood-cells were found in the urine but there was no other evidence of nephritis. Microscopic hæmaturia with occasional bouts of macroscopic hæmaturia associated with minor infections has persisted ever since. There is no evidence that renal function is impaired. The serum-proteins are normal, as is his blood-pressure. There is no hearing loss.

The mother of these boys, aged 36, is apparently well but gives a history of renal disease during her pregnancies, and her urine now contains albumin and occasional red blood-cells. Her brother (case 3) was first noticed to have hæmaturia after a cold at the age of 5 years. This recurred at intervals, and he was admitted to hospital when he was 6. The presence of blood and protein in his urine was confirmed. He was referred again at the age of 10 years on account of deafness, and he was discovered to have a 30-decibel loss on each side. His renal condition was reassessed, and it was found that he had chronic nephritis with a urea clearance only 30% of normal. During the next three years he remained apparently well apart from

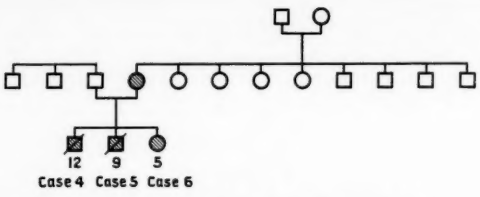

Fig. 3—Family tree of family B. For key see fig. 1.

deafness, but there was continuous microscopic hæmaturia and albuminuria and a gradually rising blood-urea and blood-pressure. He was also found to have an unexplained retinal detachment on the left side. He died at home at the age of 13. Postmortem examination was not made. Another sister is alive and has two healthy children; but a younger brother, aged 19, is very deaf and is also said to have kidney disease. Their mother, aged 63, is deaf and also has chronic renal disease.

FAMILY B (FIG. 3)

A boy, aged 12 years (case 4), was admitted to hospital at the age of $2^1/_2$ years with a week's history of hæmaturia associated with tonsillitis. He was kept at rest but a varying amount of hæmaturia persisted. This was not improved by tonsillectomy, and after three months he was discharged with continuous microscopic hæmaturia which has persisted ever since. Macroscopic hæmaturia has occasionally been present in association with infections—including such virus infections as measles, mumps, and influenza. A moderate amount of proteinuria is also present. Despite this his general health and development have been excellent, and a recent assessment of renal function gave normal results. His serum-protein values are normal, but electrophoresis shows elevation of α_2 and depression of γ globulin. During the past year or so the patient has been noticed to be a little deaf, and on testing was found to have a 30-decibel loss in both ears.

Case 5, aged 9 years, the brother of case 4, first had macroscopic hæmaturia associated with a sore throat at the age of $3^1/_2$ years. There was no other evidence of nephritis apart from a raised erythrocyte-sedimentation rate (44 mm. in the first hour, Westergren). He was not admitted to hospital but has been followed up as an outpatient. The urine has always been found to contain large numbers of red blood-cells but very little protein. He has had occasional recurrences of macroscopic hæmaturia with minor infections. There is no evidence of impaired renal function. Although he has no clinical deafness, pure-tone audiometry shows some hearing loss in each ear.

Case 6, aged 5 years, the sister of cases 4 and 5, has never had any overt evidence of renal disease; but a test of her urine at the age of 10 months revealed microscopic hæmaturia which has persisted in every subsequent specimen. The number of red blood-cells (about 10–20 per high-power field) has never been as great as in the case of her brothers. She, too, has normal renal function and normal hearing.

The children's mother has had albuminuria, œdema, and some hypertension with each pregnancy, and a recent specimen of her urine was found to contain a few red blood-cells and a trace of protein. The remainder of her family are apparently well.

FAMILY C (FIG. 4)

A girl, aged 8 years (case 7), was first noted to have hæmaturia at the age of 2 years following an upper respiratory infection. There was no œdema, oliguria, dysuria, or hypertension. She was kept at rest at home for four months, but the hæmaturia persisted and she was admitted to The Hospital for Sick Children, Great Ormond Street, under the care of Dr. George Newns for further investigation. Addis counts showed that she was passing up to 80,000,000 red blood-cells per twenty-four hours as well as a varying amount of protein. The blood-urea was normal, but electrophoresis of her serum showed a rise of α_2 and a depression of γ globulin. After a further four months' bed rest it was shown that this was not affecting the amount of hæmaturia, and she was therefore

discharged. During the past five years she has remained very well, and in fact has sailed across the Atlantic and back in a small yacht without apparent ill effect. But every specimen of urine tested has contained large numbers of red blood-cells as well as an increasing amount of protein. Her blood-urea has remained normal but her blood-pressure is now 128/90 mm. Hg. She has no obvious deafness, though testing with a pure-tone audiometer does show a loss of a few decibles on each side.

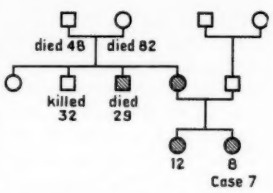

Fig. 4—Family tree of family C. For key see fig. 1.

The patient's sister, aged 12 years, is apparently well, but her urine contains both albumin and red blood-cells. Their mother's urine also contains red blood-cells and a little protein. The mother's younger brother had been unhealthy from the age of 2 years. He was discovered at the age of 19 to have renal disease, from which he died at 29. He was also increasingly deaf from the age of 12.

Discussion

There can be very little doubt that members of these three families—in all, some 14 individuals—have Alport's syndrome. In each family the pattern of the disorder is similar and corresponds closely with earlier accounts. Hæmaturia is the presenting symptom in every case. It tends to be heavy for several years and then gradually diminishes. In several cases there has been a very distinct increase with various virus infections—a feature which is not commonly found with ordinary glomerular nephritis. During the early years of life there has been no evidence of impaired renal function, but in the second decade hypertension and renal failure have become apparent. It has been possible to confirm in several cases the observation made by Chappell and Kelsey (1960) that the α_2-globulin in the serum may be increased, but the significance of this is doubtful. Each of the patients over the age of 8 years has shown some hearing loss. Only 1 has had an eye defect—a retinal detachment, which may well be unrelated to the syndrome. As in Alport's family, no affected male has lived for more than 30 years; the females are, with 1 exception, much less severely affected.

It seems remarkable that three examples of what is apparently a very rare syndrome, should have occurred in a relatively restricted population. In fact the present series accounts for more than a quarter of our cases of " acute nephritis " which still had abnormal urine at the six-month follow-up. There is no evidence to suggest that the families are in any way related to each other. It seems possible, therefore, that the syndrome may be commoner than supposed, and that, if sought, further cases will come to light. Since the prognosis for the affected males is so poor, it is obviously important that the possibility of Alport's syndrome should be considered in all cases where hæmaturia, even in microscopic amounts, continues over a long period. The diagnosis of an individual case is not easy, particularly in the early stages before deafness or renal failure have become apparent. In these cases the family history is all-important and without it the diagnosis must remain in doubt. An example of such a doubtful case is the following:

A boy, aged 13 (case 8), had an attack of abdominal pain with hæmaturia at the age of 6. After this he was found to have microscopic hæmaturia and albuminuria which persisted despite two periods of hospital treatment. There was no other evidence of nephritis, and a " surgical " condition was suspected. Nothing abnormal was discovered on laparotomy but renal biopsy showed " subacute glomerular nephritis ". Since then his general health and development have been normal; but red blood-cells and protein have been present in every specimen of urine tested, and he has had frank, sometimes gross, hæmaturia with every infection including those due to viruses such as influenza, measles, and mumps. His serum-proteins have remained normal, but his blood-urea now varies between 40 and 55 mg. per 100 ml. His blood-pressure has risen slightly to 140/100 mm. Hg. In infancy he was found to have a congenital cystic tumour of the left iris. His hearing is normal. There is no family history of renal disease or deafness.

In many ways this boy's clinical course has closely mirrored that of the cases previously described; and possibly he too has the same syndrome.

Summary

It is suggested that the syndrome of hereditary nephritis associated with deafness should be known as Alport's syndrome.

Three further affected families, in which altogether 14 individuals are involved, are reported.

This syndrome may be less uncommon than is supposed, and sporadic cases may occur.

I should like to thank Dr. George Newns, Dr. Philip Evans, Dr. A. White Franklin, and Dr. George Ormiston for allowing me to cite their findings regarding certain of the cases, and Mr. Norman McKeith, Mr. C. Remington-Hobbs, and Mr. Gordon Midgley for their reports on audiometry.

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" . . . So we are back to the need of earning more money to buy bigger and faster cars to reach the refreshing country that retreats further and further before the onslaught of our progress. . . . In the loss of leisure and the bowing to the pressures which surround us, have we not lost, too, a sense of quality? The German pastor, Dietrich Bonhoeffer, while he was imprisoned by the Nazis and awaiting death, wrote some remarkable letters and essays. On the desirability of regaining a sense of quality in our lives, Bonhoeffer wrote: 'Culturally it means a return from the newspaper and the radio to the book, from feverish activity to unhurried leisure, from dissipation to recollection, from sensationalism to reflection, from virtuosity to art, from snobbery to modesty, from extravagance to moderation.' One final question to ponder: must we doctors continue to be carried along without protest in the strong current of modern living, or can we join with Charles Morgan in spreading the belief that 'release from the pressure of existence is a means of progress'? "—ELINOR BLACK, F.R.C.O.G. *Canad. med. Ass. J.* Oct. 21, 1961, p. 940.

PLASMA-LIPIDS IN AN AFRICAN TRIBE LIVING ON A DIET OF MILK AND MEAT

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THE Samburu people of Northern Kenya live on a diet of milk and meat and are physically very active.

This report on their plasma-lipid patterns forms part of a larger study which includes measurements of body build and blood-pressures as well as electrocardiographic and other cardiovascular findings (Shaper, Williams, and Spencer 1961, Shaper 1961). We hoped to collect data which would help to explain the differences in plasma-lipid levels in different communities. In this paper we are assessing the effects of environmental factors on plasma-lipids, and are not immediately concerned with the possible relation of altered lipid metabolism to ischæmic heart-disease. Our study is an attempt to assess whether more prolonged and elaborate investigations are warranted, either in this particular society or in similar social groups still in existence in Africa.

Background of the Samburu People

The Samburu are a nomadic Masai-speaking tribe. Their social organisation is described elsewhere, with full details of their patterns of physical activity and dietary habits (Shaper and Spencer 1961).

They own cattle, sheep, and goats, and their economy and livelihood are based directly on the products of these herds. They do not cultivate the soil, though they buy some maize meal.

All males are divided into one of three groups—boys, warriors, or elders. Each belongs to a particular age-set.

Physical Activity

The stock economy and nomadic life necessitate much walking, and the impression gained is one of quiet but constant movement among people of all ages. Typically, migrations take place every six weeks or so, the whole settlement moving for 10 or 15 miles, while at certain seasons cattle may be driven for 50 or even 100 miles in search of grazing and water.

The warriors take an active part in the herding and watering of cattle and spend the rest of their time moving in groups about the countryside, finding something to interest them at distances as far as 100 miles. Individuals have been known to travel 70 miles in a day.

The elders centre their activity around their herd. When their sons are old enough to look after the herds competently, they still spend a considerable time walking in search of lost cattle or in visits far or near; and the early years of elderhood may be harsh and exacting.

Diet

Milk is the staple diet of the males and meat is the only other major item. Vegetables play almost no part at all in the diet, although a considerable variety of roots and plants are used for their medicinal properties. In the wet season, when milk is plentiful, the warriors usually drink it twice a day, in amounts up to 8–12 pints (4–6 litres) at a sitting, and a warrior may drink 10 litres in a day, though he rarely has an opportunity to do so. In the dry season the total daily intake falls to 2 or 3 litres and may be below this in a severe drought. In the wet season the warriors will subsist on milk alone; but, when milk is scarce, meat will be taken periodically—once or perhaps twice a week. The quantity eaten is difficult to estimate, but meat is the only food apart from milk which is of any caloric significance. The elders drink less milk than the warriors, and by the time a man has been an elder for ten years or so his milk consumption will be below 2 litres daily. But elders take meat in greater quantities and more regularly than either the boys or the warriors.

The Samburu have an average of 6 milk-producing cattle per person, and in theory enough milk is available in the wet season to supply warriors with up to 10 litres a day and boys, girls, elders, and wives with up to 5 litres.

Milk was obtained in different areas on six separate occasions, and these samples were possibly mixtures from several cows. Analysis showed an average fat content of 5·6% as compared with average figures of 3·7% for cows' milk and 4·1% for goats' milk (Documenta Geigy 1956). Daily intake of 3 litres for boys and elders, and 6 litres for warriors and young elders. would give 168 and 336 g. fat respectively, providing some 60% of the total daily intake of about 5000 and 2500 calories.

Clearly this fat intake does not obtain throughout the year, being higher in the wet season and lower in the dry season. Speaking of the Samburu district as a whole, milk is probably abundant for some four months of the year; it is probably sufficient for needs during a further four months; and it is insufficient during the remaining four months, when meat has to be used to supplement it. In the estimate of fat intake no allowance has been made for the meat taken, as we have not been able to make even a rough quantitative assessment; but this is an important source of food during the dry season and an additional irregular source during the rest of the year.

Until reliable data are available, no more can be said than that the male Samburu appears to take a high-calorie, high-fat, high-protein, low-carbohydrate diet—but in an intermittent fashion, because of the seasonal variation in supply. Before our visit in April, 1960, the country had had an exceptionally severe dry period, but there had been slight rain in December, 1959, and further rain in March and April.

Material and Methods

The survey was restricted to males and no attempt was made to select subjects; the sick were treated but not included in the study. The mobile laboratory was set up in three different areas, word was spread around that a clinic was functioning, and people were encouraged to come for examination. One site was near a cattle sale where Samburu from all over the district had gathered, and two sites were in remote areas where one of our party was well known to the people. Except for two warriors who were on leave from the King's African Rifles, all the men were living the nomadic tribal life we have outlined.

All subjects were weighed and had their height measured and blood-pressure recorded, and while they were being prepared for an electrocardiogram their general condition was noted, with special regard to anæmia, parotid enlargement, cardiac enlargement, pulse rate and rhythm, and auscultation of the cardiac area.

Estimation of Age

Ages were assessed by Mr. Paul Spencer, an anthropologist who had lived for several years as a member of the Samburu tribe. He assessed it by ascertaining the age-set and sub-age-set of each subject, and calculating the approximate age from known historical data concerning these age-sets. This method was

PLASMA-LIPID LEVELS (mg. per 100 ml.) IN SAMBURU WARRIORS AND ELDERS, WITH MEAN VALUES AND STANDARD DEVIATIONS

—	Warriors		Elders		All males	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Number	(102)	..	(99)	..	(201)	..
Total cholesterol	169·0	40·4	162·0	37·1	166·0	39·2
Phospholipids	209·0	37·8	215·0	32·8	212·0	34·5
C/P ratio	0·82	0·14	0·76	0·13	0·79	0·14
Total fatty acids	255·0	64·9	252·0	47·2	254·0	58·12
Triglycerides	85·3	39·8	84·7	23·9	85·0	31·9

considered accurate to within four years for almost all subjects and to within two years for the majority.

Blood Samples

Samples were taken from 102 warriors (age range 16–31 years: average 26) and from 99 elders (age range 34–80 years: average 46). As a rule they were obtained in the morning, and a note was made of the nature of any preceding meal. A light tourniquet was applied and 20 ml. venous blood was collected into dry anticoagulant (oxalate) using a hypodermic needle size 0 (length 41·5 mm.), to which was attached a length of translucent plastic tubing. The blood was kept in a refrigerator (4°C) until evening, when it was centrifuged, the plasma was separated, and it was stored at −20°C until used.

Methods

Estimates were made as follows: total cholesterol (Abell et al. 1952); lipid phosphorus (Bartlett 1959); triglycerides (Van Handel and Zilversmit 1957); and total fatty acids (Stern and Shapiro 1953). A factor of 25 was used for conversion of lipid phosphorus to phospholipids.

In the papers to which we refer in comparing plasma-lipid levels found in the Samburu with those found elsewhere, the methods used are comparable to those we have employed. But even identical methods may give different results in different laboratories and we are aware that some uncertainty is unavoidable in such comparisons.

The standard error of difference between means (S.E.D.) and the difference between the means (D.) was calculated; where D./S.E.D. was greater than 2·0, the series compared were considered significantly different (Chambers 1955).

Results

The table shows, for warriors and elders separately and combined, the mean levels and standard deviations of the four lipid components studied and the total-cholesterol/phospholipid ratio (C/P ratio). No statistically significant difference could be demonstrated between the mean plasma levels of total cholesterol, phospholipids, triglycerides, or total fatty acids for warriors and elders. A significant difference was however noted between the total-cholesterol/phospholipid ratio in warriors and elders (D./S.E.D. = 2·8).

Discussion

Plasma-cholesterol

The mean plasma-cholesterol level for all Samburu males (166 mg. per 100 ml.) is comparable to that found by Shaper and Jones (1959) in healthy young adult African males in Kampala, Uganda, living on a diet to which fat contributed 10–15% of total calories. It corresponds to that found by Bronte-Stewart et al. (1955) in adult African males in South Africa living on a similar low-fat diet. Though these three investigations were done at different times, using different (though comparable) methods, the degree of approximation of cholesterol levels in the different groups appears significant and certainly warrants a direct comparative study of the Samburu against other groups at the same time and using a single method.

The implication of most recent investigations into dietary patterns and plasma-lipids is that the dietary habits of communities are usually reflected in their mean plasma-cholesterol level, and that this rises with the consumption of animal fats. The Samburu people, however, consume much fat but have low cholesterol levels.

Phospholipids

In normal subjects the concentration of phospholipids tends to follow that of cholesterol quite closely; when one is high the other tends also to be raised, and the ratio of cholesterol to phospholipids is usually more constant than is the concentration of either component (Peters and Mann 1943).

In the Samburu males the mean phospholipid level (212 mg. per 100 ml.) is similar to that of Yemenite immigrants newly arrived in Israel, whose diet contains some 30 g. fat per day. Slightly higher levels were found in Yemenite Jews who had lived in Israel for many years and whose diet contained 55 g. fat per day (Toor et al. 1958). In normal American males levels of about 300 mg. per 100 ml. are usual (Stamler et al. 1956, Gertler et al. 1950), while in patients with ischæmic heart-disease still higher levels are noted (Stamler et al. 1956). The Samburu phospholipid levels are thus closer to those of healthy groups on diets relatively low in fat than to those of groups with a relatively high consumption of fat.

In experimental atherosclerosis the cholesterol/phospholipid ratio seems to be an important factor, and an increase of plasma phospholipids may modify or prevent atherosclerosis in rabbits (Ladd et al. 1949) and in dogs (Davidson et al. 1949). In humans, however, the use of the C/P ratio as an index of disturbed lipid metabolism has had both support and criticism (Jackson 1952). Mean levels for various groups of normal subjects have usually been in the region of 0·75 to 0·85, and there has been no significant increase with increasing age (Gertler et al. 1950, Peters and van Slyke 1946, Oliver and Boyd 1953, Stamler et al. 1956, and Toor et al. 1958). In subjects with ischæmic heart-disease and presumably a disturbed lipid metabolism, the mean C/P ratio is usually around 0·90 (Gertler et al. 1950, Oliver and Boyd 1953, Stamler et al. 1956). Despite the significant difference in the mean C/P ratio between warriors and elders, the overall C/P ratio is within the normal range.

Total Fatty Acids

The mean figure for total fatty acids in all male Samburu was 254 mg. per 100 ml., which is much the same as the 234 mg. found in South African Bantu on a diet in which 15–20% of the calories were derived from fat and contrasts markedly with the figure of 464 mg. in white South Africans who got 35% of their calories from fat and the very high figure of 718 mg. in patients with ischæmic heart-disease (Antonis 1958).

Plasma-triglycerides

Interest in the plasma-triglyceride concentration much increased when it was shown that hyperlipæmia may accelerate blood clotting, increase blood viscosity, and increase the aggregation of red blood-cells. Allbrink et al. (1959) found that plasma-triglycerides were above the "maximum" level in 5% of normal young adults, in about 30% of normal men over 50 years of age, and in 85–90% of patients with myocardial infarction. The correlation with disease was much closer with plasma-triglyceride levels than with plasma-cholesterol levels, and these workers suggest that an error in the metabolism of triglycerides is the lipid abnormality operative in coronary artery disease.

The mean level of 85 mg. in Samburu males is comparable to levels found in young American men (Peters

and Man 1943, Van Handel and Zilversmit 1957) and in both white and Bantu South African prisoners on a diet in which 15% of calories came from fat (Antonis and Bersohn 1960, 1961). White South Africans under 40 years of age and on a normal Western diet showed similar levels, but those aged 40–60 years had a mean plasma-triglyceride level of 174 mg. per 100 ml. and this rose to 196 mg. in patients with ischæmic heart-disease.

Thus the mean triglyceride levels in Samburu seem to be similar to those in healthy persons under the age of 40, irrespective of race and to some degree irrespective of diet (Peters and Man 1943, Van Handel and Zilversmit 1957, Antonis and Bersohn 1960, 1961). This observation is in keeping with experimental results indicating that, though some dietary fats produce higher cholesterol and phospholipid levels than others, triglycerides in the plasma are relatively constant and do not vary in parallel with other lipid groups (Ahrens et al. 1957). In the white South Africans over the age of 40 years the inclusion of potential atherosclerotics with abnormal lipid metabolism may well increase mean levels—a possibility supported by the very high standard deviations encountered.

Investigations into the influence of diet on plasma-triglycerides in South African white and Bantu prisoners, showed that high-fat-calorie diets, rich in their content of saturated fatty acids, raised the plasma-triglyceride levels in both these groups previously on a low-fat/high-carbohydrate diet (Bersohn and Antonis 1961). A gradual increase in mean plasma-triglyceride level, as compared to the level on their original diet, was observed after twenty-two weeks; but it was only after fifty-one weeks that the differences were highly significant. When the diet was changed so that the proportion of calories obtained from fat was 15% instead of 40%, the triglyceride level rose immediately, being far greater in the Bantu than in the white subjects. These levels subsided rapidly in the Bantu and by the twelfth to fourteenth week almost 90% were below 100 mg. per 100 ml.; but in the white subjects the return to base took far longer. This rapid return to normal levels in the Bantu was attributed to their being " naturally accustomed " to the low-fat diet.

We summarise the above work fairly fully because it may well have some bearing on the levels of triglycerides found in the Samburu despite their high estimated intake of saturated fat. It will be recalled that for probably four months of the year milk supplies are inadequate, and from time to time actual famine may prevail.

The published evidence suggests that semistarvation changes plasma-lipid levels little if at all, except for a slight decrease in cholesterol. There is no convincing evidence that plasma-lipid levels fall significantly (Keys et al. 1950). Thus during periods of semistarvation, the plasma-lipid levels of the Samburu would probably resemble those of other communities living on low-fat diets. When the rains come and milk is once more available or even abundant, the diet will again have a high proportion of fats; but the South African experiments suggest that the rise in plasma-triglycerides will be gradual. As milk supplies are seldom adequate for more than thirty-two weeks in the year, there would not be time for big increases in mean triglyceride levels.

The large seasonal variation may itself explain the low triglyceride (and possibly other lipid) levels encountered in these people living on a high-fat/low-carbohydrate diet. If this explanation is acceptable for all the lipid components measured, perhaps we need not invoke other factors.

Physical Activity

Attempts have been made to ascertain whether differences in habitual physical activity could account for the variations in plasma-cholesterol concentrations in different populations (Keys et al. 1956). It has been suggested that " a large muscle mass or a large energy expenditure is the effective agent, and that this, not the diet, is the important element in preventing hyperlipæmia " (Mann et al. 1955).

It is well established that the plasma-cholesterol level in man can be changed by altering the proportion of calories provided by fats—without change in total calories or in physical activity. But this does not exclude the possibility that physical activity may *also* affect the plasma-cholesterol level, and recent short-term experimental studies indicate that it may prevent an increase in plasma-lipids when increased fat is ingested to meet greater caloric demands (Mann et al. 1955, Keys 1956, Taylor et al. 1957).

Reviewing data from many countries, Keys et al. conclude that physical activity does not explain the *large* differences in plasma-cholesterol concentration observed between populations eating different amounts of fat. They do not imply or assert that physical activity has no effect on cholesterol metabolism but that differences in physical activity are relatively unimportant. In Finland, for example, a predominantly rural population with a high rate of energy expenditure has high levels of plasma-cholesterol and a high incidence of ischæmic heart-disease. The average amount of fat in the diet is high and the per-capita consumption of butter fat is one of the highest in the world (Keys 1957).

But though the Finns may resemble the Samburu in their physical activity, their dietary pattern is different in that fats are high throughout the year and probably throughout life.

Conclusion

The effects of physical activity in persons and groups ingesting potentially atherogenetic diets (Plotz 1959) need further investigation. As suitable for this type of study, Walker (1960) has mentioned nomads in Somaliland and Eritrea who live on the milk of goats and cows; but the Samburu of Northern Kenya, who combine high physical activity with a diet of milk and meat, also seem an ideal group for such investigation.

While their pattern of diet is certainly high-fat/low-carbohydrate, their food supply varies with the season of the year. In theory cattle and small stock are available to maintain food intake when milk is scarce; but in practice cattle are not readily slaughtered even in time of need, and imported foodstuffs (e.g., maize meal) are by custom not taken by adult males of the Samburu tribe. Thus the high-fat diet is intermittent and periods of frank inadequacy are not unusual.

The situation is similar among nomadic tribesmen in Somaliland and Eritrea. Milk is their staple food, and 4–9 litres may be drunk daily, with an estimated intake, in some groups, of some 180 g. fat per day, providing 40% of total calories (Ferro-Luzzi 1954, Egidio 1950). But every year there is a dry season lasting several months, when the insufficiency of calories sometimes amounts to a real famine.

The low levels of plasma-lipids found in the male Samburu are probably not due entirely to their physical activity but mainly to the intermittency of their high-fat/low-carbohydrate diet. They suggest that a high intake of butter fats or other saturated fats does not raise blood-lipids to abnormal levels unless it is habitual—perhaps part of a life-span pattern of diet.

We should point out, however, that ours has been an uncontrolled pilot study. For definite conclusions, seasonal studies are necessary and direct comparisons must be made with other groups in East Africa.

Without the energy and initiative of Mr. Paul Spencer, of the East African Institute of Social Research, this work would not have been possible; we are deeply grateful to Prof. A. W. Williams and Dr. P. G. Wright for their invaluable cooperation.

The study was made possible by grants from the United States Public Health Service (H.4791), Makerere College Research Grants Committee, and the East African Council for Medical Research. We wish to thank the District Commissioner, Samburu district, for permission to conduct this survey in Maralal–Wamba area.

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EFFECT OF TOLBUTAMIDE ON PERIPHERAL ARTERIAL DISEASE

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DRAMATIC relief of pain in 34 out of 36 cases of thromboangiitis obliterans during treatment with tolbutamide was reported by Singh and Brara (1960). The major symptom in a third of these 36 patients was intermittent claudication. Tolbutamide has also been shown to relieve the pain of cardiac ischæmia (Singh and Bardhan 1959, Fabrykant and Ashe 1960). Pain in these two conditions is generally due to diminution in muscle blood-flow, and this mechanism applies also to the claudication pain in atheroma.

On this basis a double blind trial was planned to evaluate the effect of tolbutamide on peripheral arterial disease due to atheroma. Intermittent claudication was the criterion for selection. In assessing the effect of tolbutamide, reliance was not placed on subjective change alone; clinical examination, ergometry, oscillometry, and skin temperatures were used as objective indices of change.

Plan of the Trial

A double blind trial was carried out. 36 patients were originally selected, the common factor being ischæmic pain on exercise in one or both lower limbs.

4 patients were lost from the trial at an early stage when they failed to keep appointments. Of the remaining 32 patients 6 completed only the first half of the trial. Thromboangiitis obliterans was diagnosed in 1 case: the patient presented with thrombophlebitis, and arterial biopsy showed inflammatory changes. The remaining patients all had atheroma. In every case the diagnosis was confirmed by aortiography, which showed a localised or diffuse iliac or femoral block in those with unilateral disease, and involvement of both sides or the aorta in those with both legs affected.

Identical-looking placebo tablets and tolbutamide tablets were placed in numbered containers by an independent observer. The patients were given these containers at monthly intervals, and it was arranged that each patient had either active or placebo tablets for the first or second three-month period. Neither the patients nor the personnel concerned knew at any time which tablet any patient was receiving. The active tablet contained 0·5 g. tolbutamide, and the patient was instructed to take three tablets daily.

The patients were seen monthly. At each visit they were questioned about ischæmic pain with special reference to claudication distance, severity, distribution, and the presence or absence of rest pain. Note was also made of any untoward symptoms in the previous month. During these visits the legs were examined and records made of the impression of the skin temperature and colour, of the presence or absence of peripheral pulses, and of any signs of ischæmia. Each patient was weighed, and venous samples were taken for the estimation of blood-sugar. Finally, the claudication distance was recorded on a fixed-wheel bicycle. In this test, the load varied from case to case but was the same at each visit for any one patient. Constant pedalling-rate was obtained by using a metronome as a pace-maker.

Before each patient was admitted to the trial, and in each of the subsequent three-month periods, a more detailed series of tests was carried out. In these tests an attempt was made to produce maximal, and therefore comparable, blood-flows through the lower limbs at rest. A constant-temperature room was used for the tests. After a rest period of a few minutes, synchronous oscillometric recordings were made of the peripheral pulses in the lower limbs. The cuffs and machine settings were placed in the same position on each occasion, in order that the amplitude of the pulse waves could be compared; an electronic multi-channel direct-recording machine was used. Skin and muscle temperatures were also recorded using thermocouples strapped to the skin and inserted in the calf muscles; again particular care was taken to use the same sites on each occasion. A standard indirect heating test was then performed by wrapping the patient's trunk in blankets and immersing the arms in warm water for 20 minutes. The water temperature was constantly adjusted to 44°C. The oscillometric studies and temperature readings were repeated after heating.

It is appreciated that these attempts to measure maximal blood-flow through the lower limbs at rest do not approach in accuracy techniques involving the use of plethysmographs; but we considered that these more exact methods were impracticable in a trial of this nature. Moreover, it would have been desirable to measure the blood-flow through the legs during exercise, but again this is more easily done on the fit young subject than on the elderly patient with claudication. Because many of these patients had had lumber ganglionectomy performed previously on one or both sides, a comparison of the records of one patient with those of another or even, in many cases, of one limb with another is not acceptable. Throughout this trial the aim was to record the presence or absence of circulatory change in each limb, and rigid precautions were taken to ensure that all

conditions were the same at each visit. The same observer interviewed the patients and carried out all tests.

Results

The results are shown in the accompanying figure. Subjective change was the patient's own impression of his symptoms during the previous month. Objective change and ergometry were assessed by examination and the use of the fixed-wheel bicycle, as already described. Any change in these observations was recorded as a percentage, and 25% change in one or other direction was considered to be improvement or deterioration respectively. Some cases described as unchanged might have been improved at one visit and worse at another while on the same tablet. In the oscillometric and temperature studies, an alteration of 5 mm. Hg in pulse-pressure or 1°C temperature variation were accepted as significant change.

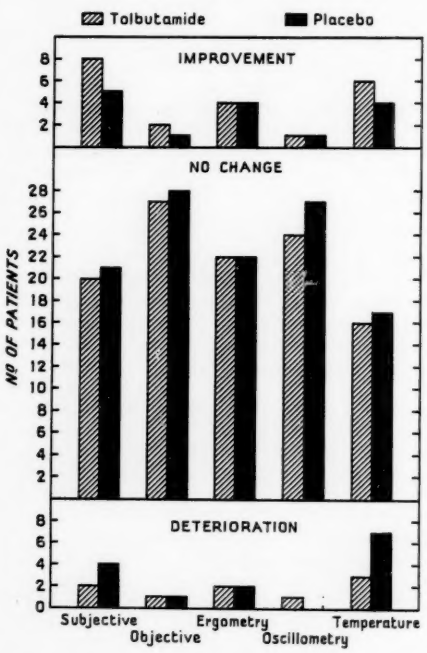
Study of these figures shows that tolbutamide did not influence peripheral arterial disease in any of the parameters studied. The total results are summarised in the accompanying table.

No side-effects were noted during administration of tolbutamide. Symptoms of hypoglycæmia did not occur, and the lowest blood sugar recorded was 50 mg. per 100 ml. In no case during the trial was there a weight change of more than 7 lb. 1 patient had an exacerbation of a quiescent peptic ulcer while receiving tolbutamide.

In 3 patients with cardiac pain in this series, this also was unaffected by tolbutamide.

Discussion

Tolbutamide did not improve this series of patients with peripheral arterial disease. This finding is disappointing when compared with the dramatic improvement reported in thromboangiitis obliterans (Singh and Brara 1960) and ischæmic cardiac disease (Fabrykant and Ashe 1960, Singh and Bardhan 1959). Singh and Brara reported diminution of pain in all cases of intermittent claudication within a few days, and observed that the effect persisted for from one to seven weeks after withdrawal of treatment. In the present trial the same dose of tolbutamide was used, and neither immediate nor delayed improvement was found to result. In seeking to explain the relief of ischæmic pain by tolbutamide administration, Singh suggested that the drug prevented the local formation or accumulation of pain-producing metabolites. The result of this trial does not support this hypothesis.



Findings in patients showing improvement, no change, and deterioration during the trial.

EFFECT OF TOLBUTAMIDE ON PERIPHERAL ARTERIAL DISEASE

Tablet	Improved	Unchanged	Worse
Tolbutamide	9	16	3
Placebo	6	19	4

Summary

32 cases of peripheral arterial disease with intermittent claudication were treated with tolbutamide 0·5 g. three times daily. A double blind trial was carried out, and the patients were assessed subjectively and objectively by various means. The effect of tolbutamide was essentially similar to that of placebo tablets, and tolbutamide is considered to be without value in this condition.

We are grateful to Hoechst Pharmaceuticals, and particularly to their English distributors, Horlicks Ltd., for supplies of 'Rastinon' and placebo tablets.

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POLYMYALGIA RHEUMATICA
A MISNOMER?

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IN the past few years several workers have described a syndrome, observed in middle-aged or elderly persons, characterised by poorly localised pain across the shoulders and neck muscles and in the chest, lower back, buttocks, and proximal parts of the arms and legs. The pain is accompanied by morning stiffness. Constitutional upset may or may not be present. One feature that has been regularly noticed is that the shoulder-girdle, and to a less extent the shoulder-joint movements, are limited in range; and usually there is tenderness over the acromioclavicular and sternoclavicular joints, though the patients are often unaware of this until it is discovered on examination. Spinal movement is usually limited and percussion of the spinal column painful. The erythrocyte-sedimentation rate is often increased disproportionately to the constitutional upset. Serological tests for the rheumatoid factor are negative in the great majority of cases. No specific radiological changes have been noted and muscle biopsy has proved unhelpful.

Forestier and Certouciny (1953) described twenty-five cases of this syndrome, which they considered to be a periarthritis and called *pseudo-polyarthrite rhizomélique*. Kersley (1951) and Bagratuni (1953) had both described similar cases; and Barber (1957) described a further group of cases of this syndrome, for which he suggested the term "polymyalgia rheumatica".

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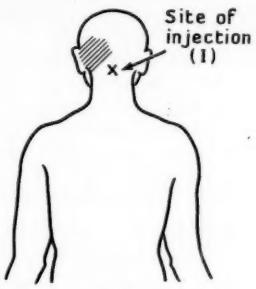

Fig. 1—Distribution of pain in two subjects after injection of 0·2 ml. 5% saline into C1-2 interspinous ligament.

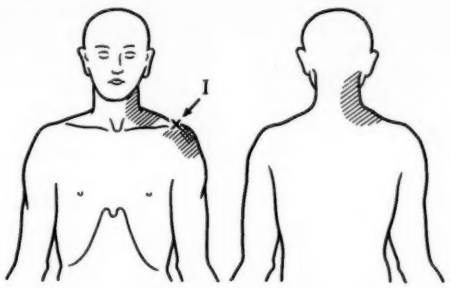

Fig. 2—Distribution of pain in four subjects after injection of 0·2 ml. 5% saline into acromioclavicular joint.

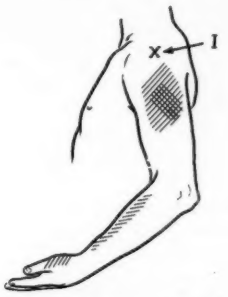

Fig. 3—Distribution of pain in two subjects after injection of 0·2 ml. 5% saline into subacromial bursa.

Gordon (1960), in another study, noted tenderness of the tissues over the front of the shoulder and over the sternoclavicular joints; he did not find swelling of these joints, but noted transient swellings in the metacarpophalangeal and knee joints in some cases.

In this unit numerous patients have been seen whose illness fits this clinical description and in whom the central joints were slightly limited in movement and painful and in some cases swollen. In such cases central polyarthritis was diagnosed. Accordingly we decided to produce a painful stimulus in central joints and ligaments and observe the type and distribution of pain.

Method of Investigation

The investigation was carried out on five subjects. The sites investigated were the shoulder-girdle joints, the subacromial bursa, the manubriosternal joint, the interosseus sacroiliac ligaments, and the atlantoaxial interspinous ligament—the last two of these sites were chosen because of the impossibility of making an injection accurately into the upper cervical apophyseal and sacroiliac joints. The distribution of pain arising from some of these sites has not been studied previously.

The technique was that described by Kellgren (1938). The skin overlying the structure to be studied was anæsthetised by intradermal injection of 1% procaine in order to avoid skin pain from leakage of the subsequently injected saline solution along the needle track. A gauge-18 needle was then introduced into the structure under study; 0·2–0·3 ml. of 5% saline was injected slowly and the needle removed. The subject marked out on a standard body-chart the area where he felt pain, and its point of greatest intensity. Saline produces pain, but does not lower the threshold to mechanical stimulus, so that pain is not aggravated by movement or pressure on the part stimulated. In order to avoid fatigue, not more than two structures were studied at one session.

Results

Interspinous Ligament C1-2

Two subjects were injected. The area of referred pain was the same in each (fig. 1). It comprised a dull, deep, unilateral occipital headache of even intensity; it was difficult to localise, and extended to the ipsilateral mastoid process. Coughing and sneezing made no difference, but movement seemed temporarily to relieve the pain which returned to its original intensity immediately the head was held still. This distribution of the pain was that observed most frequently by Campbell and Parsons (1944) in similar experiments.

Acromioclavicular Joint

The injection was given here in four subjects with the shoulder-joint held in full external rotation in order to facilitate accurate injection. The pain appeared about 15 seconds after the withdrawal of the needle. The area of maximum pain was over the top of the shoulder but spread slightly downwards over the upper part of the deltoid muscle and up the side of the neck as far as the mastoid process (fig. 2).

Subacromial Bursa

This was injected in the same manner in two subjects who sat with the arm hanging naturally at the side. No pain was felt at the site of the injection. Pain was maximal over the lower part of the deltoid muscle and was present to a lesser degree at the base of the thumb (fig. 3). No pain was felt in the elbow region.

Sternoclavicular Joint

This joint was injected from its superior aspect in four subjects. After the injection pain was severe and almost immediate. Localisation of the pain (as had been noted on previous occasions) was not as easy and the site of its greatest intensity varied between subjects, but the total areas of reference were very similar. The pain was felt over the joint and over the sternomastoid muscle up the side of the neck to below the jaw, and also in a small area over the trapezius muscle, which in one subject was the point of maximum pain (fig. 4).

Manubriosternal Joint

This was injected in two subjects—in one case to the left and in the other to the right of the midline. No pain was felt at the site of the injection, but as the injection was being given one subject experienced an indefinite widespread pressure over the front of the chest. In each case the injection was followed by unilateral deep pain about two costal spaces lower than the joint, the pain being greatest about the nipple line or just inside it (fig. 5). It felt as if breathing was going to hurt, but a deep breath had no effect.

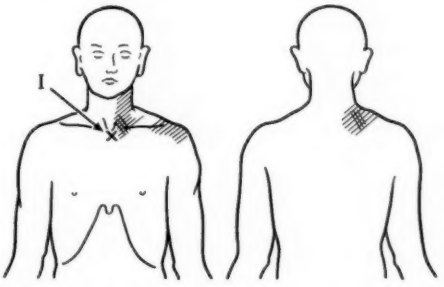

Fig. 4—Distribution of pain in four subjects after injection of 0·2 ml. 5% saline into sternoclavicular joint.

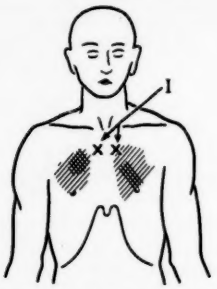

Fig. 5—Distribution of pain in two subjects after injection of 0.5 ml. 5% saline into manubriosternal joint.

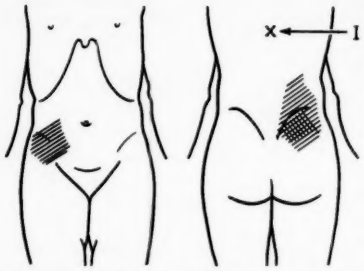

Fig. 6—Distribution of pain in two subjects after injection of 0.2 ml. 5% saline solution into T12-L1 interspinous ligament.

Interspinous Ligament T12-L1

This ligament was injected in two subjects, who were later to have the sacroiliac ligament injected. In view of the distribution of pain from this structure previously described (Kellgren 1938), we wished to compare this with that arising from the sacroiliac ligament. No pain was felt at the site of the injection; pain was greatest over the upper part of the buttock on one side, spreading slightly upward and rather indefinitely into the loin, and was accompanied in one case by pain in the corresponding groin (fig. 6).

Interosseous Sacroiliac Ligament

This was injected in the upper part in one subject and in the lower part in two others. In the first case, a dull ache was felt in the upper part of the buttock and in the groin (fig. 7*a*). In the others there was a more intense pain, maximal in the centre of the buttock; there was a transient ache in the groin in one of these (fig. 7*b*).

Discussion

Pain arising from lesions of spinal and limb-girdle joints is not recognised as such but is felt "in the muscles". In the experiments described here most of the pain following stimulation of joint structures was felt over the muscle masses, often at some distance from the site of the injection. In this way it resembled the pain produced by saline injected into the infrascapular fossa, which is a deep boring pain poorly localised in the region of the deltoid muscle with no local component over the scapula. By contrast, intradermal injection of saline produces a pain localised to the site of the injection and of recognisably different quality, the sensation resembling the sting of an insect.

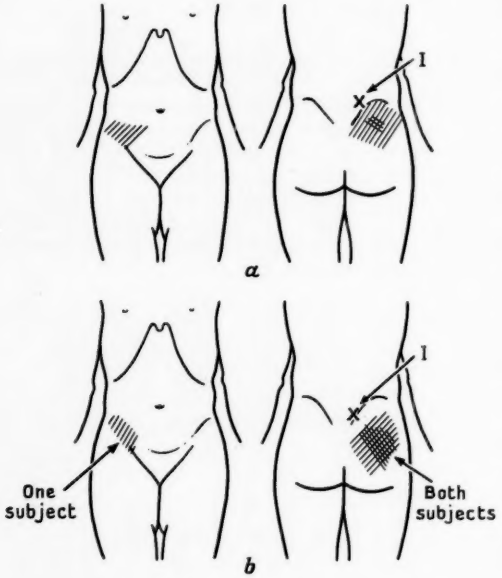

Fig. 7—Distribution of pain after injection of 0·2 ml. 5% saline into sacroiliac ligament: (*b*) one subject; (*a*) two subjects.

Kellgren (1939) ascribed such findings to faulty localisation of pain from deep structures not represented in the normal body-image. Sinclair et al. (1948) suggested that accurate localisation of pain required a certain density of nerve-supply in the structure stimulated, diffuse pain being associated with low density of innervation; faulty localisation resulted from nerve-trunk stimulation, and the attempted stimulation of deep ligamentous structures in the back by injection of saline resulted in irritation of the nearby branches of the posterior primary rami of the spinal nerves. As evidence for this they cited the observation of Kellgren (1938) that the injection of 0·3 ml. methylene-blue solution into cadaveric muscle produced discoloration of the muscle over an extent of 2 × 3 × 1 cm., and pointed out that a similar volume of saline injected into the region of the interspinous ligament might stimulate the nearby posterior primary ramus of the spinal nerve. This assumes that solutions injected into ligament and into muscle would spread similarly in extent. This is unlikely. Furthermore the concentration of saline at the periphery of the infiltrated area might be expected to be lower than in the centre, owing to dilution by body-fluids; and injection of saline in concentrations lower than 2% produces little or no pain (J. H. Kellgren, personal communication). This concept can hardly explain the pain following injection into the infrascapular fossa, which is referred to the deltoid area, since no nerve runs between these areas. And in the case of injection of interspinous ligaments, irritation of the posterior primary rami of the spinal nerves could not account for pain being referred to the front of the trunk. Inman and Saunders (1944). in observations on 160 subjects, confirmed the findings of Kellgren (1938–39) and also emphasised the difference in character between pain resulting from stimulation of the skin and that from deeper structures, and that the distribution of the latter was unrelated to individual major peripheral nerves. We therefore felt that the distribution of pain resulting from chemical stimulation of central joints and ligaments was likely to be similar to that produced by active inflammation of these structures.

In "polymyalgia rheumatica" pain is felt to be in the muscles, and attention has been focused on them as the primary site of the disease; but muscle biopsy in Gordon's (1960) cases did not show any consistent abnormalities. Pains with a similar distribution in patients without evidence of inflammatory disease were until quite lately often attributed to "fibrositis" because the pain was felt in the muscles. The results of the present investigation suggest that it is unnecessary to postulate a primary abnormality in the muscle in all such cases, since pain of this distribution may be referred from the joint structures and ligaments predominantly of the spine and limb-girdles, which are less readily accessible to

examination than the peripheral joints. In ankylosing spondylitis pains referred to the muscles are common, but the limitation of spinal movements is usually more easily observed than in this syndrome. The site of the main pathological processes in ankylosing spondylitis is generally recognised as being the joints and other structures of the spine, and it seems probable that the main pathological processes in the syndrome of "polymyalgia rheumatica" are also in the joints and ligaments of the spine and limb-girdles.

Conclusions and Summary

The distribution of pain following the injection of 5% saline solution into the acromioclavicular, sternoclavicular, and manubriosternal joints, the interosseous sacroiliac ligament, the atlantoaxial intraspinous ligament, and the first lumbar interspinous ligament has been studied.

The distribution of pain from these sites is similar to that in "polymyalgia rheumatica". In view of this, and of the failure to demonstrate any consistent muscular abnormalities in polymyalgia rheumatica, it is suggested that this syndrome is probably a form of arthritis affecting predominantly the spine and limb-girdles.

We thank Dr. W. M. O'Brien, Mr. P. H. Bennett, and Dr. F. C. Araluce for their kind cooperation in these experiments, and Prof. J. H. Kellgren for his constructive criticism.

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IRON-CONTAINING ENZYMES IN THE BUCCAL EPITHELIUM

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THE symptoms of iron deficiency cannot be explained entirely by the degree of anæmia present. Epithelial changes which occur without severe anæmia and which respond to iron therapy have long been recognised (Waldenström 1938); and recently Beutler et al. (1960) have suggested that chronic fatigue in non-anæmic women may be related to inadequate iron stores. Animal studies have shown that iron-containing enzymes in the tissues may be depleted by inducing a degree of iron deficiency which does not produce anæmia (Beutler 1957, Beutler and Blaisdell 1958, 1960), and this seems to be a possible basis for some of the symptoms found in iron-deficient patients. Studies such as these are difficult in man because those organs with the highest metabolic activity are inaccessible.

Previous experience has shown that samples of buccal mucosa can be obtained repeatedly, without inconvenience to the patient, by suction biopsy (Jacobs 1960); and specimens taken in this way have been examined by standard histochemical methods for the iron-containing enzymes, cytochrome oxidase and succinate dehydrogenase. There is some indication that a few iron-deficient epithelia show reduced cytochrome-oxidase activity.

Subjects and Methods

The following subjects were examined:

Twenty-nine apparently healthy non-anæmic adults.

Thirty patients with iron-deficiency anæmia, who all had a hæmoglobin concentration of less than 9 g. per 100 ml. and a serum-iron concentration of less than 60 μg. per 100 ml.

Five patients with megaloblastic anæmia, of whom four had classical pernicious anæmia and the other had megaloblastic anæmia of pregnancy.

Suction-biopsy specimens of the buccal mucosa were embedded in pieces of liver and immediately frozen with solid carbon dioxide:

Sections 16 μ thick were cut on a 'Cryostat' freezing microtome within an hour of taking the specimen, and they were

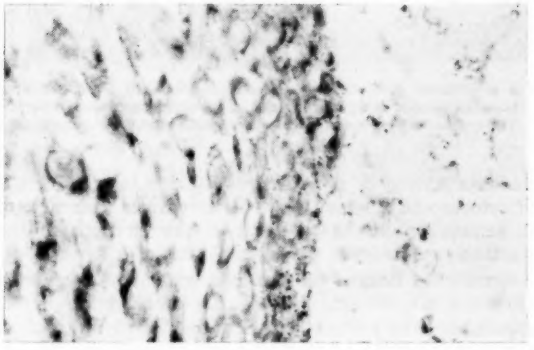

Fig. 1—Succinate-dehydrogenase activity in normal buccal mucosa. (×50.)

incubated in the appropriate substrate solution. Succinate-dehydrogenase activity was demonstrated by the nitro-BT method (Pearce 1960), the incubation-time being 60 minutes. Cytochrome oxidase was demonstrated by the N-phenyl-paraphenylene-diamine method (Pearce 1960), incubating for 120 minutes. Duplicate sections were incubated in the same medium containing in addition 0·5 mg. per ml. of cytochrome C. No counterstains were used in either method.

Results

Succinate dehydrogenase.—The sites of highest enzyme activity were marked by the appearance of dark purple diformazan granules. These were present mainly in the cytoplasm of the basal cells, and to a lesser extent in the suprabasal cells of the squamous epithelium. The cellular components of the underlying connective tissue showed a little activity. There was a blue-purple coloration of the cytoplasm of the basal cells and also of the more superficial prickle cells (fig. 1). In the most superficial squames little diformazan seemed to be formed. The degree of enzyme activity, as indicated by the amount of dye formation, varied slightly between individuals, but there was no difference between the epithelia from normal subjects and those with anæmia.

Cytochrome oxidase.—Enzyme activity in the squamous epithelium showed the same distribution as succinate dehydrogenase, being greatest in the basal cells. There was some variation in intensity of staining between different subjects, and occasional specimens showed only

CYTOCHROME-OXIDASE ACTIVITY IN THE BUCCAL EPITHELIUM

Enzyme activity	Normal	Iron-deficiency anæmia	Megaloblastic anæmia
+++	10	5	3
++	17	13	2
+	1	6	0
Sometimes negative	0	3	0
Always negative ..	1	3	0
Total no. of cases	29	30	5

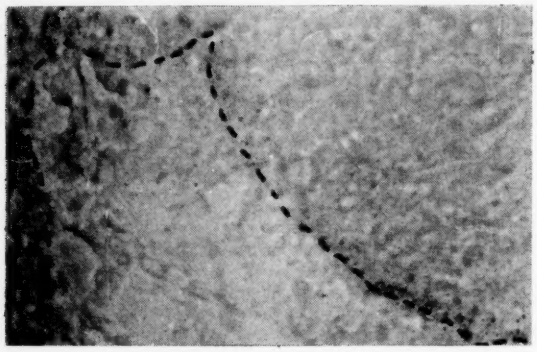

Fig. 2—Buccal epithelium in a case of iron-deficiency anæmia, showing almost complete absence of cytochrome-oxidase activity. The epithelial basement membrane is indicated by an interrupted line. (×50.)

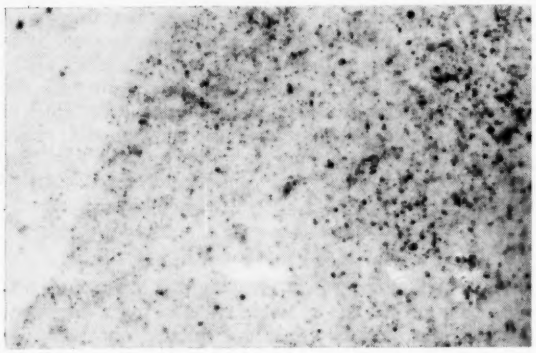

Fig. 3—Buccal epithelium from the same case as in fig. 2 seventy-two hours after 100 mg. of iron intravenously. (×50.)

traces of activity or no activity at all, even in the presence of cytochrome C which normally intensifies the reaction. A semiquantitative assessment of the strength of the reaction was made, as shown in the table.

Among the normal subjects, one was found to have no epithelial enzyme activity. Further investigation of this apparently healthy man yielded the following results: Hb 13·3 g. per 100 ml.; mean corpuscular Hb concentration 29%; serum-iron 57 μg. per 100 ml.; iron-binding capacity 420 μg. per 100 ml. Unfortunately he did not return for further investigations, but he probably had a latent iron deficiency.

Three of the patients with iron-deficiency anæmia showed no epithelial enzyme activity, and in three further patients activity was sometimes absent and sometimes present at low levels. When the first three patients were all given 100 mg. of iron ('Astrafer') intravenously, specimens of epithelium taken forty-eight or more hours later showed a normal amount of enzyme activity (figs. 2 and 3).

Epithelia from the five cases of megaloblastic anæmia showed normal enzyme activity.

Discussion

There have been repeated suggestions that iron deficiency in animals may lead not only to a reduction in hæmoglobin synthesis but also to a reduction of the tissue enzymes containing iron:

Cohen and Elvejhem (1934) found evidence that, after the induction of iron deficiency, some rat tissues were deficient in cytochrome C and cytochrome oxidase. In three iron-deficient piglets, Gubler et al. (1957) found a reduction in myoglobin concentration and a possible reduction of cytochrome C.

Beutler (1957) found a reduction of cytochrome C in the liver and kidney of iron-deficient rats, and later he showed some reduction of cytochrome-oxidase activity in the kidney (Beutler 1959). An investigation of succinate dehydrogenase revealed diminished activity in the kidneys and myocardium, but not in the liver, of iron-deficient rats (Beutler and Blaisdell 1960).

The buccal epithelium has only a very low level of enzyme activity compared with the liver, kidney, or myocardium; but its availability in man makes it convenient for study. The histochemical methods used are essentially qualitative; and the semiquantitative assessment of the reaction is, of necessity, crude. The apparent absence of enzyme activity in some cases indicates merely that the level is too low to produce a colour reaction, and this threshold level has only an arbitrary significance.

The results show that some patients with severe iron-deficiency anæmia may have a reduction in epithelial cytochrome oxidase. In three cases this seems to have returned to normal levels after the administration of intravenous iron. No alterations in succinate-dehydrogenase activity were detected. Although the enzyme deficiency may well be part of a general body depletion of iron-containing compounds, the subjects who showed this had no greater degree of anæmia or sideropenia in the blood or bone-marrow than those with normal enzyme activity. Beutler's studies indicate that patterns of activity of iron-containing enzymes may differ in various organs; and no conclusion can be drawn from the buccal epithelium regarding the state of the internal tissues or the mechanism whereby symptoms are caused in iron deficiency.

It was thought possible that the level of intracellular iron-containing compounds in squamous epithelium might be reflected by an estimation of the total iron content of an epithelial derivative, such as fingernail; and a small number of such specimens from patients with iron-deficiency anæmia indicated that the concentration might be reduced in this condition in older patients (Jacobs and Jenkins 1960). Specimens from sixty-nine adults with iron-deficiency anæmia have since been examined, and the iron content in this group was similar to that found in normal control subjects. Green and Duffield (1956) carried out a similar investigation on the iron content of human hair, and they concluded that the results give no indication of the state of the body iron stores in the individual patient. But they did note some cases where serial analyses showed that the iron level fell with iron depletion, and rose with a return to normal. The iron content of sweat is derived entirely from its cellular component, and Hussain and Patwardhan (1959) have shown that it is reduced in iron deficiency, and that it returns to normal after twenty-eight days of iron therapy by mouth.

There is no evidence that deficiency of the epithelial enzyme is associated with the atrophic changes in the buccal mucosa of some patients with iron deficiency (Jacobs 1960, 1961). Of the six patients here found to have abnormal cytochrome-oxidase activity, three had atrophic mucosæ and three were histologically normal. The subject with latent iron deficiency and apparent lack of enzyme activity had an otherwise normal mucosa. It may be that cytochrome-oxidase deficiency in the

buccal epithelium has no metabolic significance and plays no part in causing the epithelial lesions.

Summary

The histochemical demonstration of cytochrome oxidase in the buccal epithelium of normal and anæmic subjects has revealed a reduction of this enzyme in some cases of iron deficiency.

The enzyme deficiency is not apparently related to the atrophic changes in the anæmic buccal mucosa.

No reduction of succinate dehydrogenase was found.

I wish to thank the Medical Research Council for a grant supporting this work, and Miss P. Evans for technical assistance.

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NORETHANDROLONE AND PREVENTION OF PRESSURE-SORES

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PRESSURE-SORES are a perennial problem in geriatric practice, and Exton-Smith (1961) has pointed out that many factors, both intrinsic and extrinsic, play a part in their production. Loss of body-weight and a negative nitrogen balance are thought to be among these factors. In a study of paraplegic patients Cooper et al. (1950, 1951) claimed that testosterone improved the nitrogen balance because of its anabolic properties, and that this led to gain in weight and to decreased incidence of pressure-sores. We therefore decided to investigate whether or not an anabolic steroid, norethandrolone (' Nilevar '), which has been shown to cause nitrogen retention and a gain in weight among geriatric patients (Woodford-Williams and Webster 1958), would help to prevent pressure-sores in a geriatric unit.

Material and Methods

395 patients were studied in a double-blind trial. All patients admitted to the geriatric unit were accepted for the trial with the exception of those who already had pressure-sores on admission, those who could not swallow, and those who were fully ambulant.

Each patient accepted for the trial was assigned at random into the treatment or control group, and was given a serial number and an individually labelled bottle of tablets corresponding to this number. The numbers were allocated in such a way that half the patients received norethandrolone 30 mg. daily and half the placebo, for four weeks or until discharge from hospital if this occurred sooner. No-one knew which tablets were which, and the key was kept in a sealed envelope in the hospital dispensary.

The ordinary nursing routine of the geriatric unit was the same for all patients. They were got out of bed into a chair whenever possible, and efforts were made to keep the bed free of crumbs and other foreign bodies. Wet sheets were changed at least every four hours, and heels were protected from pressure by cantilever-type bed-cradles. The patients had their backs rubbed four times a day with talcum powder if they were dry, or sprayed with a silicone spray (' Rikospray ') if they were wet. Each patient had a daily wash, but the excessive use of soap on pressure areas was avoided. ' Ripple ' mattresses were not used prophylactically during the trial, but they were used in the treatment of certain patients when pressure-sores became established.

The patients were examined daily, records being kept on a special form of the state of the skin and the degree of incontinence. Patients were classed as incontinent on any day in which they had one or more wet beds. If the patient had some completely dry days the incontinence was classed as intermittent; but if not, as habitual. All patients who were fit enough were weighed weekly in a chair-type weighing-machine.

Sores were counted as superficial when they were limited to erythema, blistering, or an abrasion not involving the full thickness of the skin. They were counted as deep when the whole thickness of the skin was involved. Sores involving the whole thickness of the skin often involved the deeper tissues also, and were usually accompanied by a slough.

Results

When the key was consulted, it was found that 197 patients had received norethandrolone (treated group) and 198 the placebo (control group). The two groups were comparable in respect of age, sex, disease, incontinence, and body-weight, as well as in the proportion of patients who did not complete the full four-week trial period, because either of death or of earlier discharge from hospital.

The incidence of pressure-sores in the two groups was almost identical. The treated group had 32 patients (16%) with sores, which in 3 (1·5%) were deep. The control group had 33 patients (16·5%) with sores, which in 4 (2%) were deep.*

Weight Changes

The weight changes of 157 patients who completed a full four-week trial are shown in the accompanying table.

WEIGHT CHANGE IN 157 PATIENTS TREATED FOR 4 WEEKS

Weight change	Treated group			Control group		
	M	F	Total	M	F	Total
Gained	21	25	46	14	20	34
Lost	8	18	26	20	18	38
None	2	5	7	5	1	6

More patients gained weight than lost it in the treated group, and more patients lost weight than gained it in the control group. These figures, which are the only ones showing any material difference between the two groups, do suggest that norethandrolone helped some of the patients to put on weight.

The Pressure-sores

There were no significant differences between the 32 patients with sores in the treated group and the 33 with sores in the control group.*

A hundred and eleven pressure-sores occurred in these 65 patients. Among the 58 patients with superficial sores the lesions were single in 35 and multiple in 23. Among the 7 patients with deep sores the lesions were single in 3 and multiple in 4. All the deep sores appeared at sites where the lesion had originally been regarded as

* Fuller data on the composition of the control and treated groups and on the pressure-sores may be had from *The Lancet*, 7, Adam Street, London, W.C.2.

superficial, but in some cases the superficial stage did not last more than forty-eight hours.

In more than half the patients the sores developed during the first week in hospital. More sores began during the first week than in all the subsequent three weeks of the trial together.

Incontinence appeared to increase the liability to sores. Incontinence occurred in 69% of the patients with pressure-sores, but in only 28% of those without sores.

There was a tendency for sores to occur in those who were underweight. Among 136 patients weighing less than 8 st., 34 (24%) developed sores; but among 223 patients weighing more than 8 st., only 26 (11·5%) developed them.

The commonest site for sores was over the ischium, followed by the sacrum and heels. The trochanter and ankles were rarely affected.

Side-effects

No obvious side-effects or signs of drug intolerance occurred. Patients with jaundice and carcinoma of the prostate were included in both groups without adverse reactions to the drug. No signs of virilisation were noted.

Discussion

This trial showed that norethandrolone in a dose of 30 mg. daily for up to four weeks is of no value for the prophylaxis of pressure-sores. Formal nitrogen-balance studies were not made; but the drug did appear to encourage weight gain, and in view of previous work on the anabolic properties of norethandrolone we can assume that it favourably influenced the protein metabolism of the treated patients. Our investigation suggests, however, that improvement in protein metabolism is not a factor in the prevention of pressure-sores.

The prevention of pressure-sores remains primarily a question of nursing. The standard of nursing at our hospital is good. A 16% incidence of bedsores may sound high; but only 1·75% of the patients developed deep sores, and we counted as superficial sores many small lesions that might have been missed if we had not been on the look-out for them. Even so there is an obvious need to reduce the incidence. As Guttmann (1955) emphasised, the problem is to protect the patient from the effects of long-continued immobility. Exton-Smith and Norton (1960) have claimed that it is possible to pick out those who are at special risk in this regard, and Bedford et al. (1961) have shown that the management of such patients is likely to depend increasingly on mechanical aids such as the ripple mattress. Drugs are never likely to be more than an incidental element in treatment.

The distribution of the pressure-sores and their high incidence in the incontinent and underweight patients was perhaps to be expected, but we did not expect to find such a high incidence of sores during the patients' first few days in hospital. The sores were not present at the time of admission, when very strict precautions were taken to exclude from the trial any patient who arrived with pressure-sores, however slight. Evidently the first week is critically important for every new geriatric patient, and nursing staff should redouble their efforts during this time.

Summary and Conclusions

395 new patients in a geriatric unit were treated with norethandrolone 30 mg. daily or a placebo for a period of up to four weeks from the time of admission.

After a double-blind trial the incidence of pressure-sores in the treated and control groups was found to be almost identical, suggesting that norethandrolone is of no value for the prevention of pressure-sores.

Patients treated with norethandrolone showed some tendency to gain weight, and no toxic effects were observed.

The pressure-sores occurred most commonly over the ischia, and there was a higher incidence in patients who were incontinent and underweight.

More than half of all the pressure-sores occurred during the patient's first week in hospital, and this period is evidently of particular importance for the geriatric patient.

We are grateful to Dr. G. R. Venning, medical director of G. D. Searle & Co. Ltd., for the supply of 'Nilevar' tablets and the placebo, as well as for assistance with the expenses of the trial; and to Mrs. K. S. Pajwani for assistance with the analysis.

It is a pleasure to record our debt to the nursing staff of the Hastings Geriatric Unit. But for their devoted efforts the incidence of pressure-sores would have been much higher.

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LIVER-FLUKE INFECTION IN MAN

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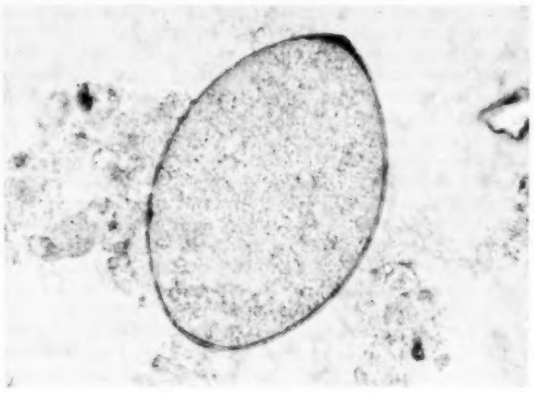
AMONG the less obvious disadvantages of an unduly wet summer is a greater risk of human and animal infection by the liver-fluke *Fasciola hepatica*. Though the animal infestation-rate is high at all times—with perhaps 30%–90% of all sheep and cattle excreting ova—in a wet year the heaviness of infection in the individual animal increases greatly. This increase is caused, not by greater contamination of pasture land by ova—for all pasture land is heavily infected in this way regardless of the weather—but by larger numbers of the intermediate host, the snail *Lymnæa truncatula*, and by the longer survival on herbage of encysted cercariæ from these snails.

In France the medical profession now recognises that wet summers are likely to be followed by sporadic cases and in some years by epidemics. In the Lyonnais region several hundred cases occurred after the wet summer of 1956 (Coudert and Triozon 1957). Since conditions for infection of man are probably at least as favourable in this country as in France, it seems remarkable that more cases are not recognised here. But until Facey and Marsden (1960) described 6 cases in Hampshire after the wet summer of 1958, only 16 cases had been recorded, and in most of these the condition was unexpectedly discovered during surgery. I now record 2 further cases.

The Cases

In October, 1960, a farmer's wife had slight pain in the left lower chest and a temperature of 99·6°F. On Nov. 3 left basal rales were noted, and a course of terramycin was given with no effect. The temperature was swinging to 101°F, with evening rigors and night sweats. The patient was then admitted to hospital. On Nov. 20 the pain shifted to the right chest on breathing, and by Nov. 22 rales were heard at the right base. On Nov. 30 a right upper-abdominal mass was found which later proved to be the liver. On Dec. 3 the liver edge was palpable to the umbilical level. The temperature continued to swing to 101–103°F. Despite numerous investigations, the only positive findings were a high and persistent eosinophilia,



Ovum of *F. hepatica*. (×370.)

and a serum alkaline phosphatase raised to 35 units. Fæcal examinations were negative for ova until Jan. 11, 1961, when scanty ova of *F. hepatica* were found (see accompanying figure).

Diagnoses considered were hydatid disease, atypical Hodgkin's disease, and eosinophil reticulosis.

As soon as the diagnosis of fascioliasis had been made, emetine hydrochloride 40 mg. was given by intramuscular injection daily for ten days (total dosage being 6·7 mg. per kg body-weight). Improvement was immediate. This was followed by chloroquine, 450 mg. daily for three weeks after a loading dose of 300 mg. t.i.d. for three days.

Ova were absent from the fæces six days after emetine treatment was commenced, but on concentration a few were once again found on Jan. 30 and Feb. 1. The fall in eosinophils is

FINDINGS IN THE PATIENT AND HER HUSBAND

Date	Total leucocytes	Total eosinophils	Fasciola ova in fæces
The Patient			
Nov. 16	9900	4356	Absent
Dec. 3	12,000	4560	,,
,, 20	15,000	5550	,,
Jan. 9	11,000	5060	,,
,, 11	Emetine commenced		Present
,, 13	..	8300	,,
,, 18	14,000	8048	,,
,, 24	..	4943	Absent
Feb. 2	..	3875	..
,, 7	..	2187	Scanty
,, 13	7000	1112	,,
March 2	6000	637	Absent
,, 21	6000	506	,,
April 20	5200	444	,,
The Husband			
Jan. 23	..	4875	Absent
March 2	9000	4687	,,
,, 21	10,000	4106	,,
April 20	6000	562	,,

shown in the table. Careful examination of all fæces after treatment failed to show any liver-flukes.

This case well exemplifies the diagnostic triad of pyrexia, hepatomegaly, and upper-abdominal pain, which in the presence of eosinophilia should suggest the invasive period of liver-fluke infection.

Source of Infection

The patient lives in a farmhouse on the side of a low hill, much of which was grazed by sheep. Springs drained into a boggy area behind the farmhouse where watercress grew. This watercress was eaten by the family during September and October, 1960.

After the diagnosis of this patient, her family was examined.

Two sons had normal eosinophil-counts. On Jan. 23, 1961, however, the patient's husband was found to have a count of 4875. On questioning, he admitted to having had vague abdominal discomfort during the previous autumn. Repeated fæcal examinations failed to demonstrate ova of fasciola. The eosinophilia persisted unchanged until the end of March and thereafter rapidly fell. It seems likely that spontaneous cure had taken place, the migrating larvæ either dying before reaching the bile-ducts or perishing before reaching maturity.

Such spontaneous cures are probably frequent. Lavier and Marchal, writing in 1942, said that only 21 cases of fascioliasis had been reported in metropolitan France. After the 1956 summer several hundred cases were reported, but this enormous increase was due to more general recognition of the clinical picture and to systematic investigation of family and other contacts of known cases. A high proportion of these were either symptom-free or had very slight symptoms. It is thus quite certain that many cases of fasciola infection undergo spontaneous cure.

Discussion

These two cases—one proven, and one probable—increase the number of cases recorded in this country to 24. One case was recorded from the Kent and Sussex Hospital by Ward in 1911, and others in the Ringwood outbreak in 1959. More than half the total have been found accidentally at operation, usually for gallbladder disease, where adult flukes were seen in the larger bile-ducts. The symptoms and signs of the acute infective stage—pyrexia, upper-abdominal pain, hepatomegaly, and eosinophilia—arise during the invasive period when larvæ, having penetrated duodenal wall and entered the liver, are ploughing their way through liver tissue to reach the bile-ducts.

The source of infection is almost always watercress, and it is a mistake to suppose that, while wild watercress is dangerous, cultivated watercress is safe. There is no public-health inspection of commercial watercress beds, and they are not kept snail-free. Whether *L. truncatula* in or out of watercress beds is infected by fasciola depends on the presence of nearby grazing sheep and cattle, and whether cultivated watercress is infected by encysted cercariæ is a matter of chance.

Diagnosis

In all suspected cases of liver-fluke infection the most important investigations are examinations of fæces and blood. Ova are unlikely to be found in the fæces until at least twelve weeks after infection. Before they can be demonstrated some at least of the migrating fluke larvæ must have reached the major bile-ducts and become mature adults: the stormy period of migration through the liver will be nearing its end and the symptoms may be subsiding. During the twelve-week invasive period the most helpful diagnostic pointer is eosinophilia, and liver-fluke infestation should always be suspected when a high eosinophil-count is associated with the symptoms and signs described above. An onset during late autumn and winter is significant.

Lavier (1942) stated that eosinophilia reaches its maximum about four months after infection, and thereafter falls slowly during a period of years, being cut short by treatment with emetine. Coudert and Triozon (1957) believe that in untreated cases the eosinophilia remains constant for several months, then falling slowly to reach a normal level after one to two years. Of the 2 cases here described, the treated case showed an immediate fall in eosinophil level which reached normal after three months.

The untreated case maintained a high eosinophil level for four months; this then fell quite as rapidly as in the treated case.

The third diagnostic test, much employed in France, is the intradermal test; but the antigen is not obtainable in this country.

Summary

Two further cases of *Fasciola hepatica* infection in man are recorded.

The risk of cercarial infection of watercress is increased by a wet summer.

Possible liver-fluke infestation should be considered in all cases where pyrexial illness is associated with a high eosinophil-count—particularly in autumn and winter.

I gratefully acknowledge help given in the preparation of this paper by Dr. W. M. Ramsden, physician to the Kent and Sussex Hospital, who treated the patient while in hospital, and by Dr. D. B. Hitchings, the patient's family doctor.

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PLEURAL EFFUSION AND RHEUMATOID DISEASE

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THE association between rheumatoid arthritis and pleural effusion is of considerable clinical interest. The presence of a common ætiological factor responsible for the two conditions, when coexisting, is not yet universally accepted despite a well-documented study of 9 cases by Horler and Thompson (1959). Added support for the view that the two disorders have a common origin was given later by *The Lancet* (1960) which, although remarking that it was perhaps arguable that the relationship was no more than that of a precipitating factor, concluded that the series of Horler and Thompson gave convincing additional evidence that rheumatoid pleural effusion was a clinical entity.

I describe here a group of cases of pleural effusion in which the sheep red-cell agglutination test (S.C.A.T.) was positive.

Material

The series consisted of 7 males observed for periods varying from fifteen to thirty-nine months. All patients had radiological evidence of pleural effusion, but in 2 this was not confirmed by aspiration; all had a positive S.C.A.T. Of the 7 patients 2 have not so far developed rheumatoid arthritis; in 2 others the effusion preceded the development of the arthritis; and in the remaining 3 the joint symptoms came first. In only 1 case were there parenchymal lesions in the lungs; the patient was a miner showing radiological appearances of Caplan's syndrome. Reasonable care was taken to exclude other conditions, especially tuberculosis and bronchial neoplasm, as a cause of the effusion. In 2 cases needle biopsy of the pleura was done, helping to exclude these diseases but not providing histological evidence of rheumatoid disease; L.E. cells were sought but not found, and the subsequent course made unlikely a diagnosis of systemic lupus erythematosus.

Case-records

Case 1.—A motor mechanic, aged 50, was admitted to hospital for investigation of a large right-sided pleural effusion. He gave a history of dyspnœa, small hæmoptyses, and anorexia in the preceding month. No previous respiratory or other illness. X-ray examination confirmed the presence of an effusion which on aspiration was straw-coloured. A total of about 5 pints of fluid was removed during the ensuing seven weeks. No malignant cells were seen, nor were acid-fast bacilli grown on culture of the fluid or sputum. Guineapig inoculation of the fluid was negative on two occasions. Pleural biopsy showed histological evidence of chronic pleuritis, the pleura being infiltrated with macrophages; there was no evidence of tuberculosis or carcinoma. Bronchoscopy and bronchography were unhelpful. In the eighth week of his illness the patient developed severe articular pain with effusions into both knee-joints, pain and swelling of both wrists, finger-joints, and right elbow. The erythrocyte-sedimentation rate (E.S.R.) was 60 mm. in the first hour (Westergren); S.C.A.T. positive at titre of 128; no L.E. cells found. Radiography of the knees and hands showed soft-tissue swelling of left knee-joint and of the proximal interphalangeal joint of the right middle finger.

The patient was treated with cortisone; no further aspiration of the pleural cavity was needed, and after three months he was discharged on a maintenance dose of methylprednisolone. Radiography twenty-eight months after admission showed erosions in the head of the proximal interphalangeal joint of the right middle finger, with general periarticular demineralisation of both hands. Cervical spine normal. He remained reasonably well apart from articular pains, returning to work six months after admission. S.C.A.T. remained positive (titre between 128 and 512) throughout thirty-eight months of observation.

Case 2.—A 38-year-old coalminer referred to outpatient clinic on account of joint pains present for six weeks in hands and arms and right knee. Six years previously found to have pneumoconiosis and removed from coal face to haulage work. Examination of joints showed only limitation of movement of wrists and shoulders. Chest X-ray revealed typical appearances of Caplan's syndrome. E.S.R. 24 mm. in first hour; S.C.A.T. 32.

The patient was treated with salicylates, and after four weeks his condition was unchanged. A month later he returned ill, febrile, with swelling and redness of wrists, knees, and finger-joints. There was clinical evidence of a right-sided pleural effusion which on aspiration was straw-coloured, the predominating cells being polymorphs; guineapig inoculation negative and no malignant cells seen. Pleural biopsy showed the appearance of acute inflammatory fibrinous deposit on chronic thickening of the pleura: S.C.A.T. 32. Treated with prednisone and discharged improved after four weeks; joint condition fluctuated but effusion did not reappear, and he returned to work six months after admission. Methylprednisolone was substituted for prednisone at sixteen months, and X-rays of hands then showed demineralisation of carpus and of metatarsophalangeal and interphalangeal joints with soft-tissue swelling of middle and ring fingers of both sides. There was loss of joint space second metatarsophalangeal joint on left side. No erosions. He has remained at work; S.C.A.T. and latex tests continue positive. Follow-up period twenty-eight months.

Case 3.—A bricklayer's labourer, aged 39, referred owing to severe pain at lower end of sternum for ten days. Pleural rub heard right side, and chest X-ray showed obliteration of right costophrenic angle; Mantoux test positive; sputum culture negative for acid-fast bacilli. Admitted to hospital two months later, when radiologically small pleural effusion had developed on the right side. No biopsy done, as little fluid was obtained; but fluid culture was negative for acid-fast bacilli.

The patient was considered to have tuberculous effusion and was treated with antituberculous drugs for six months. After fifteen months' observation pleural rub returned with onset of polyarthritis involving hands, wrists, knees, and elbows. S.C.A.T. 1024. Treatment with salicylates was started. Rheumatoid

nodules appeared on both elbows at twenty-nine months, when erosions were visible radiologically on juxta-articular part of proximal phalanges 4th and 5th digits right hand. Continued to take salicylates; usually managed to work during follow-up period of thirty-nine months, at end of which S.C.A.T. was 512.

Case 4.—A bricklayer, aged 25, became ill with fever, aches and pains, and some diarrhœa. Shortly severe pain in the left chest and breathlessness was noted; after three weeks he was admitted to hospital febrile and with a left pleural effusion. No family history of rheumatoid disease. E.S.R. 35 mm. in first hour. Mantoux test negative 1/100. Pleural fluid dark-straw coloured and contained numerous polymorphs; guineapig inoculation negative. After ten days he developed an effusion in the right pleural cavity; this disappeared and he became afebrile.

Three weeks after admission both effusions had gone, and the possibility of rheumatoid disease was first considered. S.C.A.T. positive at 512. Discharged after one month having had no specific treatment; S.C.A.T. 128. At home he developed pain in left shoulder, knees, and wrists after five days, and his own doctor treated him with a three-week course of cortisone acetate. He returned to work, and apart from some aching in shoulders remained well. S.C.A.T. became negative on discharge, and after five months there was no abnormality on X-ray of hands and feet; cervical spine showed loss of joint-space c2–3. Followed up for fifteen months.

Case 5.—A labourer of 57 developed aching in fingers of both hands and was referred to hospital a month later on account of a febrile illness with pain of pleuritic type in the right chest, having had a temperature of 103°F for two days. Chest X-ray showed a small right pleural effusion. Joints appeared normal. The chest pain disappeared in a week, and repeat X-ray after three weeks showed only pleural thickening. Joints slowly worsened, and at six months there was spindle-shaped deformity of fingers and limitation of movement of right knee. Radiographs of hands at that time revealed erosions in right proximal interphalangeal joints 2nd and 3rd digits, and narrowing of joint space left metacarpophalangeal joints 2nd and 3rd digits. S.C.A.T. 32. Soluble aspirin gave relief and the patient was working. S.C.A.T. still 32 at twenty-four months, becoming negative at twenty-six months after onset. Followed up for thirty months, at end of which S.C.A.T. and latex test were negative.

Case 6.—A man, aged 48, who had been unable to work for two years on account of rheumatoid arthritis, was admitted to hospital urgently, febrile and complaining of two weeks' breathlessness with pain in the left chest. Both his mother and father were said to have had a similar arthritis. The changes of moderately severe nodular rheumatoid arthritis were present in the hands and wrists, and to a lesser extent in the feet. Nodules over sacrum. Extreme dyspnœa, and signs of bilateral pleural effusion confirmed radiologically. E.S.R. 38 mm. in first hour; S.C.A.T. 128. Various antibiotics were given, appearing to make little difference to the fever which settled over six weeks, and gradual improvement occurred. Many aspirations of each pleural cavity were needed; fluid was sterile on culture and negative to guineapig inoculation. No L.E. cells found. Discharged after fourteen weeks greatly improved and not dyspnœic; joint pain controlled by soluble aspirin, and thirteen months after admission S.C.A.T. was 512. Then limitation of neck movements started. Radiography at that time showed multiple erosions in carpus and most of the metatarsophalangeal joints and interphalangeal joints 2nd to 5th digits both sides. Feet similarly affected. Cervical spine: demineralisation with several disc degenerations and loss of space atlanto-axial joint. Fully ambulant and not breathless when followed up at twenty months; S.C.A.T. negative at that time.

Case 7.—A joiner, aged 66, who gave a past history of a perforated duodenal ulcer, having no family history of rheumatoid arthritis, was seen in consultation at his home. Nine days before he had had sudden left-sided chest pain with no respiratory symptoms. Fever for two days. Signs of pleural effusion on left side found clinically. Attended outpatient clinic a week later, when chest X-ray confirmed presence of small left pleural effusion; but attempt at aspiration unsuccessful. E.S.R. 25 mm. in first hour; S.C.A.T. positive 128. Radiographs of hands showed two possible erosions proximal interphalangeal joint right 3rd digit; osteoarthritic changes cervical spine with loss of disc space c6–7. Repeat chest X-ray after three weeks showed almost complete absorption of fluid; and finally the only remaining abnormality was pleural thickening. During the illness he lost about 12 lb. in weight, which was subsequently regained. At no time were there any articular symptoms, and S.C.A.T. became negative in one month and remained so when he was last seen at fourteen months.

Discussion

There has been considerable disagreement in the past about the existence of pulmonary lesions attributable to rheumatoid disease. Scadding (1956), for instance, found it difficult to accept the suggestion that there could be a single cause for coexistent lung lesions and rheumatoid arthritis. Similarly Lodge (1956) stated that in his experience pleural effusion was rare in rheumatoid arthritis except when heart-failure supervened, and Aranoff et al. (1955) concluded that there were no specific lung changes in rheumatoid arthritis. On the other hand at about the same time, Rubin (1955) stated that the commonest expression of rheumatoid disease in the chest was a small serous pleural effusion. The present series of cases supports the view that a single ætiological factor causes these two conditions.

The predominance of males in patients with these two conditions noted by Horler and Thompson (1959), of whose 9 cases 8 were men, is again evident in this series. Again, this series shows that especially in middle-aged men a pleural effusion may precede or inaugurate the rheumatoid process in the joints. In cases 1, 2, and 5 the two events were fairly closely related in time, with clinical evidence of a continuous illness in between, the effusion coming first in case 1, and the arthritis first in cases 2 and 5. In case 3 the pleurisy recurred with the onset of polyarthritis; but in case 6 bilateral pleural effusions developed only during the course of established rheumatoid arthritis. In cases 4 and 7, although there were transient articular pains in one and possibly significant radiological evidence of rheumatoid in the other, neither has developed rheumatoid arthritis during the period of observation. Moreover, in both the S.C.A.T. became rapidly negative and remained so. The diagnosis in these cases rested solely on the finding of a positive S.C.A.T., which later, when the constitutional disturbance had subsided, became negative. Kellgren and Ball (1959) pointed out that in a random sample of the population of a Lancashire town the serum factor responsible for agglutination existed in some 5% of adults; but the figure is only about 1·3% if from their 19 positive cases are excluded those with any clinical or radiological evidence of rheumatoid disease. It is arguable—and difficult to refute—that cases 4 and 7 of the present series represent this fraction of the "normal" population. But neither patient had any relative with rheumatoid disease; and I believe that there is enough clinical evidence to consider that in these 2 cases the agglutination tests were of diagnostic significance. In the past three years, with increasing awareness of the possibility of rheumatoid

disease presenting with a pleural effusion, the S.C.A.T. was done in 12 cases where initially an effusion could not be adequately explained. In only 2 instances (cases 4 and 7 of the present series) was this test found to be positive; in the others a satisfactory explanation of the pleurisy was subsequently discovered.

There is little doubt that rheumatoid arthritis may present with an effusion into the pleural cavity, particularly in males, and that a pleural effusion may develop during the course of the established disease. Furthermore I suggest that a pleural effusion may be the sole clinical manifestation of rheumatoid disease, although in such cases arthritis may possibly develop in the ensuing years.

Summary

7 men who were considered to have rheumatoid disease, and in whom a pleural effusion developed, were observed for periods of from fifteen to thirty-nine months.

In 2 the effusion preceded the joint changes, while in 3 others articular pain was the presenting symptom; of the remaining 2, 1 had articular pain, but so far arthritis has developed in neither.

Pleural effusion is a not uncommon presenting feature of rheumatoid disease in males.

I should like to thank my colleagues, Dr. E. Beetles and Dr. M. Spink, for the radiological and histological reports respectively; Dr. W. A. L. MacFadyen, who allowed me to study 2 cases originally admitted under his care; and Dr. J. Ball, of the rheumatism research unit, Manchester, and Dr. F. Stratton, Director of the Manchester Regional Blood Transfusion Service, for doing the sheep red-cell agglutination tests.

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Preliminary Communication

SECRETOR STATUS IN CARCINOMA OF THE BREAST

SINCE an association was established between blood-groups and certain diseases, the secretor status of disease has been investigated. Clarke et al.,[1] Wallace et al.,[2] and Newman et al.[3] found a significant increase of non-secretors in patients with duodenal ulcer. The proportion of non-secretors is normal in gastric ulcer and gastric carcinoma,[3] diabetes mellitus and allergic diseases,[4] and ulcerative colitis.[5] Walther and Raeburn.[6] found no difference between the secretor status of normals and 1000 cases of malignant disease. This report is of a study of the secretor status of patients with carcinoma of the breast.

METHODS

Saliva was collected from 258 patients with known carcinoma of breast in the Dundee and Edinburgh areas. 300 control specimens of saliva were collected in Dundee from hospital personnel and patients with diagnoses other than breast carcinoma. All specimens were boiled for ten minutes, and stored in deep freeze until they were tested. Secretor status was determined by the isohæmagglutination test, using anti-H substance prepared from the seeds of *Ulex europæus*.[7]

RESULTS

There were 82 "non-secretors" (31%) and 176 "secretors" among the 258 cancer patients examined. Of the 300 control subjects, 66 were non-secretors (22%), which is similar to the expected proportion of non-secretors among healthy people [2 8]:

	Non-secretor	*Secretor*	*Total*
Control	66	234	300
Cancer patients	82	176	258
	148	410	558

Incorporating the necessary continuity correction for the 2×2 table, the observed value of χ^2 is 6·319. The appropriate number of degrees of freedom is $(2-1)(2-1)=1$. For one degree of freedom, the 5%-level value of χ^2 is 3·84. Because the observed value of 6·319 exceeds this, the difference between the proportions of subdivision of the samples of control cases and cancer patients is significant at the 5% level.

DISCUSSION

Blood-group substances are complex mucopolysaccharides which occur in a water-soluble form in the secretions of about 78% of the population. Aird et al.[9] suggested that blood-group substances present in the gastric secretions of secretor-positive patients may confer protection against ulceration of the gastrointestinal mucosa, and so explain the increased prevalence of non-secretors in duodenal ulceration. The ability to secrete is inherited as a mendelian dominant gene, and the liability to secrete is determined at the time of birth.[4] The substances are usually found in larger quantities in the milk and saliva than in the serum of the same individual. Mucopolysaccharide substances secreted in the milk may conceivably protect the breast tissues by the same mechanical or immunological action.

The results are significant enough to encourage further tests in other centres.

SUMMARY

The secretor status of 258 patients with carcinoma of the breast was compared with that of 300 normal controls. The proportion of "non-secretors" among the patients with carcinoma of the breast was significantly higher than in the control group.

My thanks are due to Mr. Walter Campbell for his help and encouragement; to Prof. Robert McWhirter for allowing the collection of specimens from his clinic; and to the board of management (Dundee area) for a grant to cover travelling expenses.

I am indebted to Mr. J. R. Gray, of the department of mathematics, St. Andrews University, for the statistical calculations.

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Medical Societies

HEBERDEN SOCIETY

THE Society's annual meeting was held in London on Dec. 1 and 2, under the presidency of Dr. F. DUDLEY HART. The Heberden Oration was delivered by Lord COHEN OF BIRKENHEAD, who was later presented with the Heberden medal for 1961.

Dr. E. HAMILTON and Prof. E. G. L. BYWATERS (Taplow), reviewing 47 cases of myelomatosis, had found disease of joints or tendon sheaths in 7, the conditions encountered being degenerative arthritis, gout, and paramyloid infiltration. 6 further cases with joint symptoms and serum-protein abnormalities included 2 of primary amyloidosis, 2 of rheumatoid arthritis and macroglobinæmia, and 2 in which a myeloma-like globulin was present without other evidence of myelomatosis.

Mr. G. PLATT (Aylesbury) described his operation for arthroplasty of knee in which the femoral condyles are trimmed to receive a stainless-steel prosthesis with a central slot to take the cruciate ligaments. The results of 27 operations were assessed after a mean follow-up of $4^1/_2$ years. Persistent severe pain, the primary indication for the operation, was substantially reduced or abolished in all cases. Range of movement was not increased, but sufficient was retained to maintain the patients' independence for sitting and negotiating stairs.

Dr. MATTHEW WILKINSON compared electrophoretic studies of 35 rheumatoid synovial fluids and corresponding sera with 26 osteoarthritic fluids and sera. The synovial-fluid/serum ratio indicated greater penetration into the synovial fluid of all protein fractions except β-globulin in rheumatoid arthritis, and this was particularly striking for γ-globulin. Detailed analysis of results, correlated with synovial biopsies, suggested active secretion of γ-globulin into rheumatoid joints, such as might be expected in an autoimmune disease.

Dr. DUDLEY HART reported the results of a 30-month multicentre controlled trial of gold treatment in rheumatoid arthritis. At the final assessment there were 77 patients in the treated group and 82 in the control. In the treated group considerable improvement was found by all criteria except radiological up to the 18th month (1 year after completion of the course), but by the 30th month most of the advantage had disappeared.

Dr. E. N. COOMBS (Manchester) had found lateral instability of all 37 rheumatoid knee-joints he had examined. In contrast, no instability was found in knees actively involved in ankylosing spondylitis, and instability was infrequent in psoriatic arthropathy.

Dr. B. M. ANSELL, Prof. E. G. L. BYWATERS (Taplow), and Dr. J. S. LAWRENCE (Manchester), from clinical, radiological and serological studies of the grandparents, parents, and siblings of 93 children with Still's disease, postulated that Still's disease may result from a double inheritance—namely, spondylitis and seronegative rheumatoid arthritis.

Dr. A. ST. J. DIXON and Dr. P. H. N. WOOD reported further observations on salicylate-induced gastrointestinal bleeding. Bleeding was detected in 70% of subjects receiving aspirin or its salts, and its occurrence did not appear to be related to the presence of peptic ulceration or achlorhydria, which some were known to have. They suggested that bleeding occurred during absorption of the salicylate and was unrelated to the presence of particles on the mucosa.

Dr. C. H. LACK (Stanmore) discussed the possible role of plasmin in mesenchymal disorders. When plasminogen was injected into an ear vein of a rabbit it appeared to be activated in situ, and some loss of cartilage matrix coincided with a rise in serum and urinary chondroitin sulphate. This was sometimes followed by the disposition on vascular endothelium of fibrin-like material which might be a complex of fibrinogen and chondroitin sulphate. It resembled the fibrinoid deposits of the generalised Swartzman reaction.

Reviews of Books

The Coming of the Welfare State

MAURICE BRUCE. London: B. T. Batsford. 1961. Pp. 307. 35*s*.

THIS is a short, competent, well-written account of the social history that culminated in the great changes which became effective in this country on July 5, 1948. The author's thesis is that the Welfare State has developed to meet particular needs in the empirical manner characteristic of our society: the decisive event in its evolution was the second world war, coming as it did after a long period of distress and puzzled endeavour at relief. The years of active thought and planning were those from 1941 to 1948, "an epoch in British history". The first stirring of social conscience lay much further back—with the abuses of the poor-law children, the official attitude to poverty, apathetic when not repressive, the work of Chadwick ("that remarkable and powerful, if disagreeable and tactless, personality"), who was almost alone in his recognition of the need for "collateral aids" to poor-law reform, chief among them attention to the health and living conditions of the poor. One of the points established by developments in the poor-law field was the need for greater public provision of hospital services, free from any hint of charity or relief: another, emphasised by Newman in evidence to the Royal Commission of 1905, was the need for unification of the public medical services, with disease regarded as a "nuisance" to be removed "quite irrespective of poverty and destitution". But Lloyd George, when he introduced his National Health Insurance in 1911, made no attempt to link the service he was creating with the existing public-health services under the Local Government Board; probably, as the author suggests, Lloyd George's dislike of Burns (and his officials) played a considerable part in this decision, which he later regretted.

Perhaps the most useful service of this book to the medical reader is that it brings the Health Service into focus and perspective as an element in the broad social canvas of our time. That the service has made a great contribution to the commonweal there can be no doubt, despite its obvious enough imperfections. Its problems, and probably its lines of development, must be viewed in relation to broader questions of social policy. What, we may ask with Mr. Bruce, are we going to make of the Welfare State and of the society for which it was designed?

Lectures on the Methodology of Clinical Research

MAX HAMILTON, M.D., D.P.M., external scientific staff, Medical Research Council. Edinburgh: E. & S. Livingstone. 1961. Pp. 139. 21*s*.

THIS book contains twelve edited lectures whose central theme is the application of statistics in medicine. It is extraordinarily difficult to persuade doctors to think in mathematical or even arithmetical terms, and to learn statistics there is no escape from the hard way of slogging at exercises and in fact "do it yourself". The examples given in this book have a psychological flavour indicative of the main interests of the author. Many useful statistical techniques are described, and the pill is sweetened by an easy style of writing and much wise commentary on the necessity for depth of thought as well as technical proficiency. The pitfalls are well delineated, and he points out the dangers of complete reliance on statistical help for experimental planning. "Clinical experiments cannot be designed by experts on experimental design but only by clinicians" (p. 38). The author shows a full appreciation of the difficulties of blind and double-blind trials, the subjective errors which may arise in ranking methods, and the difficulties which can often crop up in matching individual cases in sequential analysis.

It is doubtful whether anyone who does not already know something of the use of statistics could grasp its techniques from this book. Those who already understand and use practical statistics will find the work interesting and thoughtful. Without being profound, it is certainly readable. For beginners in

research it may point the way to further interest and study, and for those with more experience it contains a good deal of wisdom and warning.

Escape and Survival

Editor: P. BERGERET. London. Pergamon Press: 1961. Pp. 117. 45*s*.

THIS is not, and is not intended to be, a book for the general medical reader. It is a collection of monographs published for the Advisory Group for Aeronautical Research and Development, North Atlantic Treaty Organisation. The editor is a distinguished Belgian specialist in aviation medicine.

The monographs are of uneven quality. The better ones have made an uneasy transition from the lecture-hall to the printed page: one is so turgid that it is almost unreadable. Yet there is a good deal to interest the specialist in aviation medicine, for the subjects the book covers are all live issues in the air forces and many also in civil aviation. A Canadian paper on R.C.A.F. survival training is particularly good. There are some rather unexpected titles: " early diagnosis of hydrops of the labyrinth " and " the role of elective surgery in a modern air force " make odd bed-fellows with " biological problems of escape at high altitudes ". One must admire the courage of the surgeon who told a gathering of aviation-medicine experts that " . . . if the raison d'être of an Air Force is properly appreciated, and if it is accepted that aviation itself—whilst it may affect physiology and psychology—has no apparent relevance to pathology, then the real problems for an Air Force medical service are to be found in the mundane fields of clinical medicine and surgery ".

The book is indifferently indexed but otherwise well produced.

Psychotherapeutic Techniques in Medicine

MICHAEL and ENID BALINT. London: Tavistock Publications. 1961. Pp. 236. 21*s*.

THIS book, in the series of Mind and Medicine Monographs, is a companion to *The Doctor, His Patient and The Illness* by Dr. Michael Balint, published in 1957, which drew solely on experiences with general practitioners. Now he uses experiences with various specialists, with doctors in charge of the Family Planning Association's special clinics, and with a group of psychoanalysts engaged in a research on " focal " therapy.

The work is divided into four largely independent parts. The first, on the influence of the setting, discusses psychotherapy by non-psychiatrists, the setting for psychotherapy in general practice, and for the specialist; and it evaluates the results in terms of efficacy and use of medical man-power. The advantages of the general practitioner's continuous contact with his patient are examined, and his variable role is shown to be of immense therapeutic potential. By comparison, the role of the specialist is seen to be ephemeral, detached, and more restricted, but also more dramatic and authoritative.

Part two, on some common problems in psychotherapy, discusses the aims of psychotherapy for patient and for doctor. Examination by the patient of his illness, in cooperation with his doctor, is judged to be the road to insight. The doctor, too, needs to be aware of his own emotional reaction to the patient, to be objective but not aloof. The doctor's responsibility is discussed, and there is an important chapter on the place of psychotherapy in medicine. These first two parts of the book are designed, as the authors say in an introduction, to awaken interest in non-psychiatrist psychotherapy, in the hope that psychiatrists will find proof that this subject merits their attention, and that general practitioners, who have come to realise that many of their patients are in need of psychiatric help, may be encouraged to acquire the necessary skills.

Part three, on theoretical considerations, contains chapters on understanding people professionally, enabling people to understand themselves, and variants of psychotherapy. Part four, on the psychiatric interview, compares this with medical examination and psychological testing, and discusses the problems of the interview and the limitations of our knowledge about the efficacy of the techniques used.

Much of the teaching is illustrated by case-reports presented at research seminars. They hold the reader's attention, and he is impelled, like the participants, to find out more and more about the patient and about his own reactions to the patient.

Surgical Treatment of Unequal Extremities

CHARLES WEER GOFF, M.D., associate clinical professor of orthopædic surgery and lecturer in anatomy, Yale University School of Medicine. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 184. 88*s*.

Two thousand years ago a man died in that part of North America now called Kentucky. It is remarkable that he ever reached adult life, for his left femur was so distorted by a localised bone dystrophy that it must have been only half as long as the right. It is stranger still that his skeleton should have been preserved, and it provides the earliest known example of a pathological inequality of the limbs. If such a patient came to a modern orthopædic clinic he would probably precipitate a discussion about the best treatment, and even now he could probably be offered little more than palliation of his disability.

This book reviews the problems of unequal extremities as they were seen by earlier authors, and as they have appeared in a long series of cases from the Newington Hospital for Crippled Children. Even the assessment and prediction of asymmetry presents serious difficulties, and Dr. Goff admits that, because slit scanography requires elaborate apparatus, usually some less accurate technique must be used. He describes his own approximate method, and he relies on Gil and Abbott's tables to forecast skeletal growth-rates. Operations for leg lengthening, he reports, were finally abandoned at the hospital in 1938, having produced too many serious complications. (Dr. Goff speaks quizzically of the " Procrustean methods " still employed by " a few English and Scottish surgeons ".) Techniques for stimulating bone growth by X-radiation, sympathectomy, or the implantation of irritant foreign bodies have also been discarded. The results they yielded were, at the worst, ineffective, and, at the best, unpredictable. It is evident that epiphyseal stapling, or the alternative of permanent epiphysiodesis, remain the only safe and consistently reliable operations for controlling a progressive discrepancy in limb length.

This volume is beautifully illustrated and painstakingly produced. And, in giving the best picture yet published of this recurrent problem, the author shows how far we are from solving it. For no-one can be content with a state of affairs in which an anomaly of one limb usually means an operation on its normal fellow.

A Manual of Pregnancy Testing

EDWARD H. HON, M.D., professor of obstetrics and gynecology, Lama Linda University, Los Angeles, California. London: J. & A. Churchill. 1961. Pp. 116. 36*s*.

To diagnose pregnancy from a woman's urine has become one of the important tests of clinical pathologists, and, whereas it was once relegated to a few specially chosen centres, it is now practised fairly widely. There is a long step in essence, though not in time, from using such an unspecific test as the red-cell sedimentation-rate to the highly specific Aschheim-Zondek procedure or its Friedman modification. These two tests are somewhat elaborate, and many laboratories now use frogs and toads rather than mice and rabbits.

This valuable volume explains the theoretical basis of pregnancy testing and discusses the various diagnostic systems from the point of view of sensitivity, economy, and accuracy, and the need for detoxification of the urine to be investigated. The quantitative estimation of chorionic gonadotrophin is also described, and the titres found in disturbed pregnancy are listed. There are some pages on typical technical problems in pregnancy testing, advice on keeping frogs and toads, and advice on keeping records.

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Management of Cushing's Syndrome

IN the six years since we last reviewed the treatment of Cushing's syndrome [1] opinion on this subject has become more uniform. By contrast, the nature and ætiology of the disorder are still disputed.

Clinical appraisal alone will seldom provide a firm basis for treatment.[2] In each case several important issues must be resolved. In the first place, are the clinical findings associated with demonstrably excessive or abnormal adrenocortical secretion? When this has been established, can the adrenals be shown to be primarily responsible? Alternatively, is the increased adrenocortical activity a response to an excess of pituitary corticotrophin? MCCULLAGH [3] has summarised opinion on the various mechanisms which may be responsible for Cushing's syndrome as follows:

"(1) Stimulation from the hypothalamus via the pituitary to the adrenal cortex with adrenal hyperplasia; (2) hypothalamic stimulation plus pituitary tumour; (3) autonomous pituitary tumour; (4) adrenal hyperactivity due to inherent adrenal abnormality; and (5) autonomous adrenal cortical tumour."

There are several reasonably satisfactory methods of assessing adrenocortical activity, but no single test distinguishes clearly and consistently between the state in health and Cushing's syndrome. BECK et al.[4] regard basal urinary 17-hydroxycorticosteroid excretion as still the best single index; and, while far from infallible, it has the merit of requiring no highly specialised laboratory resources. PRUNTY [5] has compared a series of tests of adrenal steroid metabolism in cases of Cushing's syndrome. He concludes that estimation of the cortisol-production rate, by a technique involving administration of cortisol labelled with a small dose of radioactive carbon (^{14}C),[6] is at present "the best available diagnostic criterion". Other tests used to confirm the diagnosis and determine treatment include assay of plasma and urinary corticosteroids, in order to demonstrate the effect of administered and of endogenous corticotrophin, and the success or failure of attempts to suppress the pituitary production of corticotrophin by administration of large doses of corticosteroids such as dexamethasone. The output of endogenous corticotrophin may be increased by administration of metopirone (SU 4885) [7] or its hydrochloride (SU 8874). Assay of corticotrophin in the blood—a much more formidable undertaking—may be expected to provide valuable information bearing on the mechanisms responsible for the disorder in the adrenal cortex.[8–10] These and other problems were discussed recently at two conferences.[11 12]

By a combination of clinical assessment, radiological examination, and selected steroid hormone assays, it will usually be possible to decide whether surgical intervention is necessary. Without treatment the prognosis of the established disease is poor: as PLOTZ et al.[13] have shown, 50% of patients or less can be expected to survive for five years after diagnosis. In the larger published series, bilateral adrenal hyperplasia accounts for 70–80% of cases, while of the remainder roughly half are due to adrenocortical adenoma and half to carcinoma. GUIN and GILBERT [14] have pointed to the high rate of adrenal carcinoma in children with Cushing's syndrome. When an adenoma is found at operation, removal of this can be expected to provide complete relief. In all but the very obese the adrenals can be approached through the upper abdomen [15]; and this procedure has the great advantage that both glands can be examined by a single exposure. For the 70–80% of patients with bilateral adrenal hyperplasia, the operation of choice appears to be total bilateral adrenalectomy. After total removal of both glands replacement therapy is now so satisfactory that the patient should only be handicapped, if at all, by the knowledge that replacement with corticosteroids will always be required. Some still prefer subtotal adrenolectomy, on the ground that this may avert the need for lifelong replacement therapy. But with this method it is impossible to be certain that the residual fragment of gland will remain viable or that its secretory capacity will suffice, especially in stress conditions; and, by contrast, there is real danger that the remnant will ultimately become so hyperplastic as to call for further radical treatment. ROBERTS and LATTIMER [16] refer to 12 patients treated by total adrenalectomy on one side and 80–90% adrenalectomy on the other, and another 3 treated by bilateral subtotal adrenalectomy. At least 8 required substitution therapy, and 2 required a further operation on account of recurrence. SPRAGUE et al.,[17] reviewing the results of adrenalectomy in 116 cases of Cushing's syndrome treated at the Mayo Clinic, found that among 75 patients submitted to a subtotal procedure there were 19 definite and 3 possible recurrences within periods ranging from three months to nine years. MASON et al.[18] recommended subtotal adrenalectomy for patients over 45 years of age with a mild form of the disease; but they and most other workers agree that the operation of choice is usually total adrenalectomy.

1. *Lancet*, 1955, ii, 857.
2. Soffer, L. J., Iannaccone, A., Gabrilove, J. L. *Amer. J. Med.* 1961, **30**, 129.
3. McCullagh, E. P. *in* Proceedings of Conference on Human Adrenal Cortex, Glasgow, July, 1960 (edited by A. R. Currie). Edinburgh: E. & S. Livingstone (in the press).
4. Beck, J. C., Blair, A. J., Dyrenfurth, I., Morgen, R. O., Venning, E. H. *ibid.*
5. Prunty, F. T. G. *in* The Adrenal Cortex (edited by G. K. McGowan and M. Sandler); p. 143. London, 1961.
6. Cope, C. L., Black, E. *Brit. med. J.* 1958, i, 1020.
7. Liddle, G. W., Estep, H. L., Kendall, J. W., Williams, W. C., Townes, A. W. *J. clin. Endocrin.* 1959, **19**, 875.
8. Nelson, D. H., Meakin, J. W., Thorn, G. W. *Ann. intern. Med.* 1960, **52**, 560.
9. Davies, B. M. A., 1961, *in* Proceedings of Conference on Human Adrenal Cortex (see footnote 3).
10. Liddle, G. W., Williams, W. C. *ibid.*
11. *ibid.*
12. The Adrenal Cortex (edited by G. K. McGowan and M. Sandler). London, 1961.
13. Plotz, C. M., Knowlton, A. I., Ragan, C. *Amer. J. Med.* 1952, **13**, 597.
14. Guin, G. H., Gilbert, E. F. *Amer. J. Dis. Child.* 1956, **92**, 297.
15. Aird, I., Helman, P. *Brit. med. J.* 1955, ii, 708.
16. Roberts, M. S., Lattimer, J. K. *J. Amer. med. Ass.* 1961, **175**, 93.
17. Sprague, R. G., Weeks, R. E., Priestley, J. T., Salassa, R. M. *in* Modern Trends in Endocrinology (edited by H. Gardiner-Hill); p. 84. London, 1961.
18. Mason, A. S., Richardson, J. E., King, C. E. *Lancet*, 1958, ii, 649.

Pituitary tumours are being reported with increasing frequency in patients with Cushing's syndrome treated by adrenalectomy. SPRAGUE et al.[17] refer to 14 such cases, and NELSON et al.[8] describe 10 cases in which pronounced pigmentation of the type usually associated with Addison's disease developed; in 5 of these they found unusually high blood levels of corticotrophin. Since some of these tumours ultimately enlarge so much as to require treatment on their own account, patients should obviously be observed most carefully after adrenalectomy, especially when skin pigmentation is notable or is increasing. In the past the term pituitary basophilism was used almost as a synonym for Cushing's syndrome; but SPRAGUE et al.[17] point out that histological examination of the tumour in 8 of their cases showed that the predominant cell was chromophobe. Chromophobe adenomas were found also in the only 2 cases examined among those described by NELSON et al.[8]

Pituitary irradiation has been used by DOHAN et al.[19] to treat 12 cases of Cushing's syndrome, in 5 of which the results were excellent. SOFFER et al.[2] also claim remissions in about 50% of cases after pituitary irradiation, with or without unilateral adrenalectomy. These results compare unfavourably with those obtained by bilateral adrenalectomy.[17 20] Dr. JOPLIN and his colleagues [21] have now reported encouraging results from partial pituitary ablation effected by means of implanted gold-198. This isotope gives less intense and less localised radiation than yttrium-90, which has proved the most effective isotope for complete ablation. Of 6 patients with Cushing's syndrome treated by JOPLIN et al. with gold-198, 4 had impressive, though incomplete, remissions.

Perhaps in the future " chemical adrenalectomy " will be possible, by means of drugs such as metopirone. Meanwhile, unless a pituitary or adrenal tumour is demonstrable, total bilateral adrenalectomy offers the best prospect of cure for the patient with Cushing's syndrome. Finally it is well to bear in mind that Cushing's syndrome may be associated with a carcinoma of the bronchus, of the thymus, or of other organs.[22]

Iron in Tissues

THE introduction of an iron preparation that could be given intravenously was a considerable advance which enabled a group of patients with iron-deficiency anæmia resistant to oral treatment to be relieved effectively. But intravenous iron solution is not too easy to give, especially for the general practitioner, since it is dark-coloured and, owing to its alkalinity, any leak outside a vein causes an unpleasant reaction. Another difficulty is that some patients with resistant iron-deficiency anæmia are large, fat women whose arm veins are too often invisible. For these reasons the introduction of an iron-dextran solution that could be administered intramuscularly was welcome. It has allowed us to treat all patients who fail to respond to oral iron, and it has been useful as a time-saver—for example, in the late stages of pregnancy when there is not time to risk failure to respond to oral iron. In the form of ' Imferon ', intramuscular iron-dextran became deservedly popular. Consequently the news that the observation by RICHMOND [1] that iron-dextran could cause sarcomas in rats at the site of injection had been confirmed by HADDOW and HORNING [2] was received with dismay. Admittedly the way the iron-dextran was given to the rats and mice was very different from the way it is given to patients. For instance, the iron-dextran was given subcutaneously to the rats and mice, whereas clinically a deep intramuscular site is used and precautions are taken against any subcutaneous leakage. Then the doses given were enormous; the total body-iron of the mouse is about 2 mg., and HADDOW and HORNING gave doses equivalent to 90 to 450 mg. iron (doses immensely in excess of any therapeutic dose), and further they gave repeated injections into the same site—a course that most doctors and nurses try to avoid in their patients. Many doctors considered that, since the conditions under which the tumours had been produced differed so greatly from clinical conditions, they could reasonably continue to use imferon for those patients who needed it. Nevertheless, proper investigation of the tissue changes following injection of iron-dextran solutions was clearly desirable, and a comprehensive report on this subject has now been published by BAKER et al.[3]

A single subcutaneous injection of 0·2 ml. of iron-dextran (10 mg. Fe) in a mouse is " rapidly dispersed through the subcutis from ears to tail "; and the dispersion is general, little being found in the liver. Doses given intramuscularly spread to the subcutis, and with larger doses there is little difference in the distribution of the iron whether it is given subcutaneously or intramuscularly; but these large doses are far outside the therapeutic range. In the mouse over 20% of a large dose of injected iron is found in the liver after seven days. In rats, on the other hand, much more is retained at the injection site, and most of it is still in place after seven days. In larger animals such as the rabbit and the dog, much less iron is retained at the site of intramuscular injection and much more is desposited in the liver. Histological studies in the mouse show that there is some initial necrosis of muscle at the site of the injection, but within forty-eight hours all the necrotic muscle has been removed and in about fourteen days muscle regeneration is complete. Within twenty-four hours the iron is mostly inside macrophages and fibrocytes, but some remains attached to dermal collagen; in seven days all the iron is intracellular. Thereafter the tissue iron gradually diminishes; at three months very little iron is found after a 1 mg. dose, rather more after a 10 mg. dose. Ultimately the tissues return to normal with no evidence of residual fibrosis.

With multiple injections of large doses, other changes occur according to the amount of iron administered—

19. Dohan, F. C., Raventos, A., Boucot, N., Rose, E. *J. clin. Endocrin.* 1957, **17**, 8.
20. Horwith, M., Stokes, P. E. *Advanc. intern. Med.* 1960, **10**, 259.
21. Joplin, G. F., Fraser, R., Steiner, R., Laws, J., Jones, E. *Lancet*, Dec. 9, 1961, p. 1277.
22. See *Brit. med. J.* Aug. 19, 1961, p. 505.

1. Richmond, H. G. *Brit. med. J.* 1959, i, 947.
2. Haddow, A., Horning, E. S. *J. nat. Cancer Inst.* 1960, **24**, 109.
3. Baker, S. B. de C., Golberg, L., Martin, L. E., Smith, J. P. *J. Path. Bact.* 1961, **82**, 453.

persistent swelling, loss of hair over the site, and binding together of subcutis and muscle in an œdematous mass. Mice were given three subcutaneous injections totalling 30 mg. of iron, which is fifteen times the normal total body-iron. Histological examination of the tissues showed a striking subdermal fibrosis beginning within a week; macrophages become laden with iron and some were converted into fibroblasts, but others remained rounded. When many injections were given, dense masses of these macrophages sometimes formed and showed the appearance of the "histiocytoma" of HADDOW and HORNING. It is remarkable that after up to a total of about six injections of 10 mg. of iron into a single site, the changes were still reversible and after a year the tissues were almost normal. In rats the changes were more severe; muscle regeneration was absent and fibrosis more widespread; with multiple large doses a mass of collagen with iron-containing cells embedded in it was found. BAKER et al. believe that the changes found depend on the relation of the dose of iron-dextran injected to the bulk of the tissue receiving the injection; if the critical dose into any one subcutaneous site is exceeded—in the mouse at least six injections of 0·2 ml.—then irreversible fibrosis develops.

In man the doses given for therapy are very small compared with these experimental doses, and histological examination of the sites of iron-dextran injections shows only a few scattered iron-containing macrophages. But BAKER et al. were able to examine tissues from two patients who over a period had received several hundred times the recommended therapeutic dose. In both cases early formation of fibrous tissue was found, "but no evidence of focal fibroblastic proliferation, which we regard as the precursor of subsequent sarcomatous change".

So far tumours due to iron-dextran injections have only been produced in rats and mice after massive multiple injections, grossly in excess of any therapeutic dose. The tumours are spindle-cell sarcomas or fibrosarcomas. MUIR and GOLBERG [4] have followed the development of such tumours by electron microscopy of the tissues. The tumour tissue was obtained from the hind-limbs of four rats which had received very large doses (twenty-two intramuscular injections of 75 mg. per kg. of iron as iron-dextran). The contralateral limbs had been similarly injected but in these no tumours developed; instead a mass of iron-laden tissue formed, consisting of large iron-containing macrophages. The iron in these cells was all in the form of ferritin. A change to tumour formation was heralded by an increase in the size of the mass, and section showed the formation of a pale area in which the tumour cells were found with few iron-containing cells but much collagen between the cells. The tumour cells at first contained some iron; but this diminished as the tumour developed, and eventually there might be little iron present. MUIR and GOLBERG suggest that further studies of the genesis of these tumours may be rewarding.

4. Muir, A. R., Golberg, L. *ibid.* p. 471.

It is clear from these and other results that the risk of any tumour developing at the site of iron-dextran injections used in proper therapeutic doses is extremely small. It must be much less than, for instance, the risk of aplastic anæmia with chloramphenicol, of megaloblastic anæmia with phenytoin, or of agranulocytosis with some tranquillisers, since these effects have all followed therapeutic doses. Nevertheless, the alarm about iron-dextran has had its uses. We now have detailed studies of what iron-dextran actually does in the tissues and perhaps a new point of attack on the problem of what starts the growth of tumours. Clinically doctors will perhaps limit the use of intramuscular iron to those patients who must have it—refractory cases and those where a response must be obtained as soon as possible. The dose should be limited to the recommended amount. For imferon this is about 45 mg. of iron for every 1% (on the Haldane scale) deficit of hæmoglobin (roughly a total of 1 ml. of imferon for each 1% hæmoglobin deficit), divided into doses of not more than 5 ml. at a time, given deeply into the buttock muscles, with a new site for each injection.

Annotations

CLINICIANS' SALARIES AT CAMBRIDGE

IN November, 1960, the general board of the University of Cambridge issued a report recommending that the stipends of university officers should not depend on the faculty to which they belong. The members of the regent house, bombarded with flysheets (arguments printed and circulated in order to elicit votes for one side or the other) and saturated with discussion, voted in February, 1961, by 504 to 296 in support of the report.[1] It was admitted in the report that the development of the postgraduate medical school might be jeopardised if Cambridge, alone among the British universities, refused to pay a differential to holders of posts with clinical responsibility; but the board hoped that the first-class staff needed to set up and run the new departments would, nevertheless, be attracted to Cambridge. Since February, however, the British Medical Association has not accepted advertisements in its *Journal* for appointments in the university, and when an advertisement has appeared in *The Lancet* we have in our editorial columns reminded readers that Cambridge differs from other universities in its payment of members of the teaching staff.[2]

During the summer, the University Grants Committee and the Medical Research Council stated that they would not be able to support the proposed developments if conditions of work made it impossible to appoint the best men available. And with the change of vice-chancellor at the beginning of the new academic year, the general board found that there was now a small majority in favour of paying clinical differentials, rather than see the postgraduate medical school run down and eventually close. A new report recommending differentials was therefore issued, together with a minority report against differentials.

On Nov. 14 there was a long discussion in the senate from which it appeared that most of the upholders of

1. See *Lancet*, 1961, i, 328.
2. *ibid.* Sept. 2, 1961, p. 560.

equality of prime stipends would not object to the clinical staff being paid a differential provided that the hospital board, and not the university, produced the money. This compromise was presumed to be analogous to the scientific staff receiving fees for industrial consulting or for television appearances. However, the Ministry of Health has stated that it could not consider this arrangement; and, since the regent house's new vote on Dec. 6 and 7 was 522 to 205 against clinical differentials, the outlook for postgraduate medicine in Cambridge seems gloomy.

THE CELL IN PNEUMOCONIOSIS

"A CONFLICT of living matter with the mineral world" was the title of Prof. Albert Policard's Kettle lecture at the Postgraduate Medical School of London on Dec. 1. E. H. Kettle, who died in 1936, was, said Professor Policard, among the first to recognise the different action of different kinds of mineral dust, and the fact that all produce a reaction favourable to the development of bacteria. He was a pioneer whose ideas on the pneumoconioses are more and more being confirmed.

All forms of fibrosis start with inflammation, but the various inflammatory processes vary in quantity according to the nature of the aggressor and its amount. Mineral dusts do not cause fibrosis by direct action, nor do their dissolution products cause fibrosis. To provoke fibrosis, dusts must be absorbed into the cells by phagocytosis; the cell then degenerates, and proteolysis of the cytoplasm liberates toxic wastes which induce inflammation, and secondarily fibrosis. Thus it is the lesion of the phagocytic cells, and not a direct action of the dust, that gives rise to the fibrosis.

In their investigations at the Centre d'Études et Recherches des Charbonnage de France, Professor Policard and his colleagues have made a systematic study of the changes produced in cells which have phagocytosed different kinds of mineral particles. For this purpose they have used phase-contrast microscopy and electron microscopy for the examination of lung histiocytes which have absorbed various dusts. (Phagocytosis of dusts by polymorphonuclear cells is uncommon.) With "inert" dusts (e.g., coal, hæmatite, and titanium oxide) the particles do not appreciably modify the behaviour of the histiocyte, though its movement is slowed if they are very numerous. With quartz, even a small number of particles will immobilise the macrophage; and the exudate often contains cellular debris or collections of particles, "the remains of dead or dislocated cells". In a third type of reaction the dust causes the cell to form large vacuoles which may or may not contain the particles. Professor Policard illustrated these reactions by a film in which the movements of the cells were speeded up some sixteen times. (Regrettably, for most of the large audience, the living polymorphs, as they pushed and squeezed themselves through every cranny, rather stole the show from the dead or dying histiocytes.) Examination of the cells by electron microscopy shows that coal dust, hæmatite, titanium oxide, and diatomite (kieselguhr) do no appreciable damage to protoplasm. Some kinds of silica, however, tend to coagulate the cytoplasm. Calcium carbonide produces a specific vacuolar reaction, and so does mica; but with mica the particles are usually outside the vacuole, not inside it.

Though the problem of the action of mineral particles is being transferred in this way from the tissue to the cell, it does not change; and we do not yet know whether a quartz particle damages the cell because it throws off a toxic substance (silica) or because its surface absorbs or modifies proteins or enzymes indispensable to all life. Cytoplasm can apparently be altered by coagulation (i.e., by irreversible denaturation or by vacuolisation), or by proteolysis to more simple protein complexes. The postmortem degeneration of cells takes two principal forms—coagulation necrosis, implying suppression of all enzymes, and autolytic proteolysis involving dislocation of the cytoplasm proteins. In autolytic proteolysis there is a great deal of liberated waste—polypeptides in particular—which set off the inflammatory reaction. But it has not yet been possible to isolate this cellular waste and study its capacity to provoke inflammation and fibrosis.

After the lecture Professor Policard (described by Prof. J. H. Dible as the doyen of French pathology) was entertained to dinner in the new Wolfson building of the Postgraduate School, where the guests included many of Professor Kettle's old associates. Dr. Charles Newman, the dean, presided, and Sir Francis Fraser spoke briefly of Kettle as a person. The company included two of Professor Policard's research associates, Dr. A. Collet and Dr. J.-C. Martin.

ALONE AND AFRAID

AVIATION medicine is concerned wholly—or almost wholly—with men exposed to stress; and the aviator often has to face the stress alone. The study of the emergencies of flight is the study of man both lonely and afraid.

Many of these emergencies are a direct consequence of flight—for example, the hazards of escape by ejection seat, of explosive decompression, of anoxia, or of decompression sickness. But others are more directly related to the simple ubiquity of modern aircraft: in a time of aerial emergency the terrain below is waiting to make a further trial of the escaped airman's courage and endurance.

Apart from the ocean, there is no more daunting place in which to descend than the extremes of north or south; and this is a prospect which the aircrews of the Royal Canadian Air Force have constantly to face as they fly over the Canadian Arctic. The area, more than a million square miles, has never been completely explored, except by aerial photography. It begins where the tree-line ends, through the barren lands to the perpetual ice. In summer the weather may be warm, and the region is infested with flies and sucking insects; in winter the mercury may freeze, and, besides the snow, there are frequent thick fogs and high winds which so reduce visibility that nothing can be seen from the air or on the ground.

The way in which the R.C.A.F. trains its crews to meet such conditions is discussed in one [1] of a collection of monographs on escape and survival.[2] This account is the more interesting because, although the risks are the occupational concern of military aviators, more and more passengers are being carried in civil airliners over these same inhospitable deserts.

To arrive by parachute in the Canadian Arctic during the winter is, as it were, to pile Pelion upon Ossa: it is a second disaster before there is time to recover from the first. The thirty minutes after the landing are vital, for if the survivor is not to be disabled by the cold he must make himself some shelter in which to collect his wits and apply himself to the problem of keeping alive. Only a

1. Alexander, S. E., Fraser, J. G. Fundamental concepts in R.C.A.F. Arctic Survival Training. *in* Escape and Survival (see footnote 2).
2. Escape and Survival (edited by P. Bergeret). London, 1961. See review on p. 1340.

man who has the psychological resilience to recover quickly from the double shock of the ejection and the realisation of his plight has much chance to save himself; but, though the greater part of such resilience may derive from personal qualities, at least some can be acquired by the confidence which comes from careful preparation. The Canadian training therefore aims at a preparatory "set": it seeks to prove to the airman that his clothing and equipment are effective, and that if the Eskimo can live in the Arctic winter, so can he.

The most important moral prop to the castaway is the certainty that no expense or effort will be spared to rescue him. Before he can be rescued he must be found, and this is the most difficult part of the recovery. When the searchers had to rely on visual identification, their task was almost impossible unless the weather was clear and the survivor could attract their attention by firing flares or flashing a heliograph mirror: but now that the survival gear contains a small beacon which elicits a response from aircraft radar, a search in any weather has a reasonable chance of success.

Once he has been found, the airman can be supplied from the air; but he may have to wait a long time for the actual rescue, and he is likely to need all the resolution he can muster to face the solitude and the uncertainty. To lose faith during long spells of fog and icy gales must be far easier than to believe that help is coming. If faith goes, so may the will to live; and whether a man just waits for death or kills himself, the difference in time is not very great. The rescue, therefore, must be made as early as possible; and each successful rescue is an intellectual and spiritual reinforcement not only for subsequent survivors but also for all those potential survivors who continue to fly over the empty spaces of the Arctic. An efficient and well-publicised rescue service has a continuous effect even if it never has to be used.

BLOWING UP THE STOMACH

ONE of the drawbacks of the direct method of respiratory resuscitation is that it may cause gastric inflation; and air so introduced may come out again, and bring with it fluid gastric contents which may then be inhaled.

Little has been known of the factors which influence gastric inflation produced in this way, but Ruben et al.[1] have now thrown new light on this question. In their study the entry of air into the stomachs of anæsthetised patients was detected by the characteristic gurgle heard through a stethoscope placed on the upper abdomen. Pressures were measured in the pharynx and deep in the œsophagus, and the lowest pressures that caused air to enter the stomach were noted in various conditions.

The results show that in most cases the cardia can withstand a pressure of about 25 cm. H_2O before yielding to allow ingress of air. Altering the position of the head and neck does not much affect this figure. Usually up to 1·5 litres of air can be blown into the lungs without raising the airway pressure above 15 cm. H_2O, provided that the inflation is not accomplished too rapidly. In cases of partial upper respiratory obstruction higher pressures may be required; but most of the excess is dissipated in overcoming the obstruction, and will thus be transmitted neither to the lung nor to the cardia. Hence the use of higher pressures to overcome upper airway obstruction should not increase the risk of gastric inflation. Bronchiolar obstruction is a different matter, but this is difficult to overcome with manual methods too.

An argument for the mouth-to-*nose*, in preference to the mouth-to-*mouth*, application of expired-air resuscitation is that the restriction imposed by the nasal airway irons out pressure swings imparted to the pharynx by forceful insufflation and thus decreases the likelihood of gastric inflation. Whichever route is used, in nearly all cases adequate tidal volumes can apparently be achieved without subjecting the cardia to a pressure greater than it can withstand, provided that inflation is not hurried. Prolonging the period of inflation may impede the cardiac return and hence further embarrass the circulatory system, so a compromise must be aimed at.

1. Ruben, H., Knudsen, E. J., Carugati, G. *Acta anæsth. scand.* 1961, **5**, 107.

IMPORTED FOOD

A MINOR cause for alarm during the late war was the discovery that much of the American dried egg which we imported to add variety to our diet contained *Salmonella spp.*[1] Not only were there outbreaks of food-poisoning due to this but some species of salmonella which had never been found here before became naturalised in these islands. Since then there has been a steady flow of reports of the presence of pathogenic bacteria in imported food. No-one is better placed to discuss this problem than Dr. Greenwood Wilson, medical officer of health to the city and port of London, and in a recent lecture he made it clear that the danger is not limited to bacterial infection.[2]

Dried egg is a thing of the past, but salmonellæ are still found in frozen eggs and egg albumen. Desiccated coconut was mentioned in these pages not long ago.[3] Some batches of meat (especially boneless meat) have proved to be heavily contaminated. Much of the imported horse meat (which is "meat" under one set of regulations but not under another) is intended for animal food, but it is not impossible that some of this goes astray: many outbreaks of food-poisoning in Germany early in the century were attributed to sausages containing horse meat. Cheese may contain strains of *Staphylococcus aureus* likely to cause enteritis, and prawns often contain too many bacteria of all sorts. Imported livers—also intended as food for our pets—show cysts of echinococcus only too frequently. And tea—of all substances—may contain lead in far larger amounts than those approved by the Food Standards Committee.

A port medical officer derives his powers from regulations made under the Food and Drugs Acts, but if he relied on these alone he would not get very far. He is concerned only with food intended for human consumption; but intentions are not always fulfilled, and the byways of the food trade are devious and poorly lit. Except with the consent of the importer he can detain food for only forty-eight hours, and this is not enough for a complete bacteriological examination. If he were to order the destruction of all food which might by the stretch of a lively imagination cause human ill-health, such action would gravely impede lawful commerce and would be likely to be tested frequently in the courts. He must in fact compromise between strict scientific nicety and a Nelsonic glance. If all coconut containing salmonellæ were condemned there would be none on the market: in practice no account is taken of those species which rarely if ever cause human disease in Great Britain. At the same

1. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1947, no. 260.
2. Wilson, J. Greenwood. Paper given at Royal Society of Health, Oct. 11, 1961.
3. *Lancet*, 1961, i, 655.

time the Ceylon Government is taking steps to clean up the factories where it is prepared. Not only Ceylon but other countries from which we draw supplies have shown an admirable sense of public responsibility. Cooperation between the port and the authorities into whose area the foods pass gives a further check on the disposal of potentially dangerous food. The trade as a whole has many reasons for not importing food unfit for human use and is open to reasonable persuasion. Some countries which send us egg products pasteurise them all; but egg products which contain salmonellæ can be used with reasonable safety after processes which involve heating them to a bactericidal temperature. Tea containing lead in unwholesome amounts can be blended with other teas. Ingenuity will yield an answer to most of these problems: the important thing is to know that the problem exists.

With animal feeding stuffs the position as regards infection seems to be broadly similar.[4] The chief source of these feeding stuffs is imported proteinous residues. Salmonellæ in small numbers were present in 9% of the batches of raw materials, but in under 3% of the compounded meals. Pelleted foods from the same sources yielded 0·3% of positives. Pelleting involves moderate heating, and an increasing number of manufacturers are applying heat treatment to their raw materials.

No-one could have doubted the purity of desiccated coconut—until it was shown to have caused an epidemic of enteric fever in Australia. That sad story is a valid reason for the bacteriological examination of representative samples of all the delicacies which are imported in a raw state. Nor should we be complacent about our home-produced food: salmonellæ are not unknown in butcher's meat, and almost all seafood acquires a rich bacterial flora after landing.[5] Not enough research has been done on the methods and frequency of sampling or on the tests which are necessary to preserve the public health. (In many instances quantitative tests are called for, and quantitative bacteriology is both time-consuming and costly.) At the same time we must distinguish between real and potential risks. Dr. Greenwood Wilson's lecture is an illuminating introduction to a complex subject.

CURRICULA

CHANGES in the curricula of medical schools are very often aimed primarily (and sometimes rather vaguely) at securing "integration" or "coordination" between the subjects on the student's plate at a particular moment; but, as Prof. J. M. Yoffey remarked at last week's meeting of the Association for the Study of Medical Education, these passwords could obscure the fact that the only integration that counted in the end was what happened in the student's cortex. And Prof. C. M. Fleming was sure that the curriculum was not itself the main thing: good teachers and good students counted for more. Despite these reservations, ASME spent a profitable day in the new building of the Middlesex Hospital Medical School discussing some of the changes in the medical curriculum that had been introduced or were planned in Sheffield, Birmingham, and Glasgow, and in the Middlesex school itself.

At Sheffield, as Prof. C. H. Stuart-Harris and Dr. J. G. McCrie explained, attempts had been made to wrench the student's eyes away from examinations ahead. The final M.B. examination was now in three widely separated parts: part I (pathology, bacteriology, pharmacology, and a brief test in clinical subjects) at the end of the fourth year; part II (obstetrics and gynæcology, preventive medicine and public health, forensic medicine, child health, and special subjects) at the end of the fifth year; and part III (medicine, including psychiatry, surgery, and clinical science) at the end of the sixth year. The appointments system had been redesigned to permit the inclusion of elective periods; and the students' new freedom and wider range of interests had taken some of them as far as Cracow, Stockholm, Bonn, and the Wolverhampton Wanderers Football Club (to study sports injuries). A recurrent difficulty had been the high failure-rate (about a third) in the 2nd M.B. examination; the weaker students thereby got three months out of step and found the going all the harder. Prof. G. M. Wilson illustrated the new fourth-year integrated course in pathology, bacteriology, and pharmacology. Lecture topics were proposed in turn by the three departments; and essay-writing was a prominent stimulus to thought. One attractive feature was the exercise in the evaluation of advertisements for drugs. And when it came to the single oral examination, Professor Wilson remarked, the presence at the same table of colleagues from two other departments was a distinct deterrent to the obscurer question.

Birmingham, after the reigns of Sir Leonard Parsons and Sir Arthur Thomson, had become used to convulsant therapy in its medical faculty; and the present dean, Prof. A. L. d'Abreu, gave that as one reason why it had not proved too hard to change the curriculum. There were now no systematic lectures in medicine, surgery, obstetrics and gynæcology, or (take a deep breath, warned Professor d'Abreu) pathology. Throughout the clinical course students were encouraged to stay in hospital until teatime, and medical-school lectures were now restricted to one a day—at 4.10 P.M. An intensive introductory clinical course of six weeks was attended by all third-year students, including those who had been referred in the preceding examination. After some difficulty, an experimental tutorial scheme was introduced for second-year students, and recently extended to the third year. Birmingham's severity on the routine lecture drew from the chairman, Sir Robert Platt, a caution lest the merits of the really great lecturers, such as Sir Geoffrey Jefferson, be forgotten.

Under the direction of Prof. D. R. Newth, the Middlesex's department of biology as applied to medicine is acting as a catalyst to the whole school, as Sir Brian Windeyer put it. Certainly many of those who heard Professor Newth talking about his redesigned (and almost revolutionised) premedical course must have felt sorry they could not enjoy it themselves. His aim was to try to teach for the future—to teach the biology that would be relevant to the medicine that the students would meet in later years. For example, the identification of heterozygotes, immunological tolerance and paralysis, and D.N.A. metabolism were sure to become increasingly important. Nowadays reading *The Lancet* was made painful for many doctors by the abundance of chromosomal abnormalities: Professor Newth and his colleagues wanted to ensure that their students were spared this pain. Genetics was woefully undertaught in British medical schools today; yet in twenty years genetics would probably permeate all medical teaching.

4. *Mon. Bull. Minist. Hlth Lab. Serv.* 1961, **20**, 73.
5. See *Lancet*, July 15, 1961, p. 140.

Public Health

LUNG CANCER IN VENICE

An Epidemiological Study

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IN accounting for the increasing prevalence of lung cancer in many parts of the world, great emphasis has been placed on cigarette smoking and general air pollution. Though these factors can be studied separately, especially in rural areas, we thought it desirable to study a city population that is little exposed to general air pollution, at least as far as motor vehicles and industry are concerned. The purpose of our present study, therefore, was to investigate the epidemiology of lung cancer in such a city —namely Venice.

The old city of Venice, which had 158,460 inhabitants according to the 1958 census, is built on 117 little islands and separated from the main land by $2^1/_2$ miles of water. It is $1^1/_2$ miles from the open sea, and it is transversed by 150 canals that have an average width of 4–5 yards. The largest of these, the Grand Canal, divides the city in two. Venice has as its main source of transportation gondolas and other hand-propelled boats. Motor boats are limited mainly to the Grand Canal. Venice proper has no motor traffic. The north-western part has a parking area, the Piazzale Roma, where people coming from the mainland can park their cars before entering the main part of the city. The primary source of revenue being the tourist trade, Venice has no large-scale manufacturing except for the glass industry on the island of Murano, which has about fifty glassworks employing about 2500 workers directly concerned with glassmaking.

The Ospedale Civile Riuniti is the only hospital serving the city of Venice and the islands of Murano, Burano, and Pellestrina as well as a few smaller surrounding islands, but it does not serve Mestre, the industrial city closest to Venice. Patients outside this area, which is called "Venezia insulare", are not admitted to the hospital except in emergency or other special circumstances. Thus, the hospital offers excellent opportunities for studying a specific population.

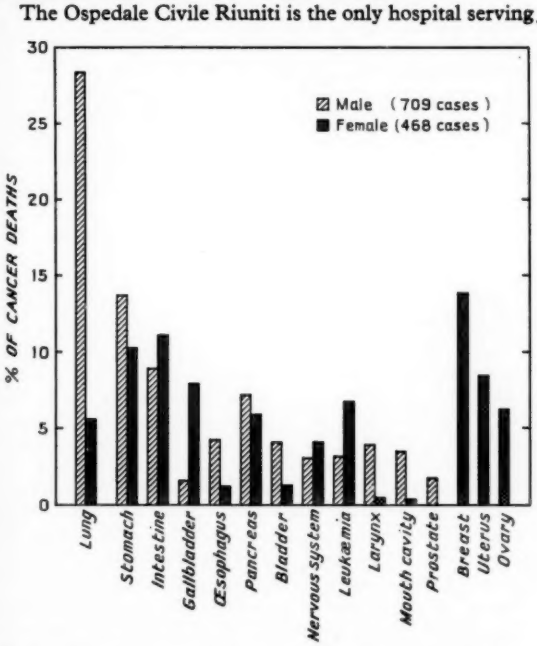

Fig. 1—Cancer cases coming to necropsy in Venice, 1951–59. Each site is represented as a proportion of the total.

The hospital deals largely with clinic patients and insured patients, only 5% being private patients. Because there is no thoracic clinic, and no thoracic surgery is done at the hospital, patients with problems requiring thoracic surgery are not specially selected. The high necropsy-rate of the Venetian hospital permits accurate study of the relative frequency of the causes of death. During 1956–59 the deaths in the hospital numbered 3396, representing about 28% of all deaths in the area covered by our study. Of this number 2609 (77%) came to necropsy.

Results of Necropsy

Necropsies at the hospital during 1951–59 showed that lung cancer was the most common cause of death from cancer among males (28%), whereas it was an uncommon cause among females (5%) (fig. 1).

TABLE I—AMOUNT OF SMOKING IN CIGARETTES PER DAY *

Amount smoked	Male controls (200)	Male patients (63)	Female controls (100)	Female patients (6)
Non-smokers	29%	8%	87%	2†
1–9 cigarettes per day ..	13%	6%	7%	
10–20 " " " ..	45%	44%	5%	3†
21–34 " " " ..	10%	27%	0	1†
35+ " " " ..	4%	14%	1%	..

* 1 cigar = 5 cigarettes, and 1 pipe = $2^1/_2$ cigarettes.
† Number rather than %.

The prevalence of most cancers in Venice is similar to that of the rest of Italy, but there are some exceptions. Stomach cancer, for instance, is especially common in the northern farm areas of the Po valley, and relatively rare in the southern part of the country. Among Venetian female cancer cases at necropsy, breast cancer is commonest, followed by cancer of the uterus. In Italy as a whole stomach cancer is commonest, followed by breast and uterus. Cancer of the gallbladder is relatively common among Venetian women, and this deserves further study. Among Venetian men, lung cancer represents the most frequent cause of cancer deaths, while for Italy as a whole stomach cancer is followed by lung cancer.

Smoking in Italy

Studies of Italian smoking habits during 1957 showed that, of Italian men over 16, 30% were non-smokers, 55% smoked cigarettes regularly, 6% smoked cigars, 4% smoked pipes, and 5% smoked only occasionally. Among women, 6% smoked cigarettes regularly, 4% smoked only occasionally, and 90% did not smoke at all.[1]

In the city of Venice, including the surrounding islands and Lido but excluding Mestre, 1,003,760 kg. of tobacco was smoked during 1958 (about 1·3 kg. per person per year).[2] The per-capita consumption of tobacco in Italy during 1958 was 1·07 kg. per person. It is our impression that the average Italian smokes his cigarette to a relatively short butt length.

THE STUDY

Controls

We interviewed, at the Ospedale Civile, 200 men and 100 women whose age distribution was similar to that of the lung-cancer patients but who had no diseases related

1. Nuovi Studi sulle Abitudini e Preferenze dei Fumatori Italiani. Doxa, Istituto per le Ricerche Statistiche e l'Analisi dell'Opinione Pubblica. Milan, 1957.
2. Statistiche sui Consumi dei Tabacchi, nell'Esercizio 1950–59. Amministrazione Autonoma dei Monopoli di Stato, 1959.

to the respiratory tract. We obtained data on their smoking habits (table I), length of residence in Venice, and occupations:

29% of the male controls were non-smokers, 64% smoked cigarettes, 1% smoked pipes, 3% smoked cigars, and the remaining 2% smoked a mixture of pipes, cigars, and cigarettes. Of the smokers, 81% smoked more than 10 cigarettes per day, and 19% smoked over 20 a day (or the equivalent in pipes and cigars). The women smoked much less than the men. 87% did not smoke, 6% smoked more than 10 per day, and only 1% smoked over 20 per day.

Most of the men and women interviewed (91%) had resided in Venice for at least twenty years. Of the men whose occupation was known, 73% were labourers and 27% were white-collar workers. Table II shows the proportion of patients in work which involved industrial exposure.

Analysis of the type of illness in 13 of the glassworkers in Murano showed no predilection for any particular disease. We also studied some environmental factors. A visit to a representative glass factory showed the quarters where the glass is produced to be relatively clean. Inspection of the roof showed little visible condensation, though it had not been cleaned for at least seven years. The oven which stands at the centre of the room is now heated with methane gas, reaching a maximum temperature of 900°C. Until seven years ago it was heated during the day with dry wood and at night with methane gas, but we were told that even in those days, because of adequate ventilation, the air was not noticeably contaminated with smoke particles. But the workers are certainly exposed to heat, and obviously in any study on diseases in the Venetian population, one would want to know whether glassworkers were particularly often affected.

TABLE II—OCCUPATIONS AND SELECTED INDUSTRIAL EXPOSURES IN VENETIAN MALES

—	Controls (200)	Patients (63)
Occupations:		
White-collar	27%	13%
Labourers	73%	87%
Specific Industrial Exposures:		
Glassworker	6·5%	9·5%
Cabinet maker/carpenter	3·5%	3·2%
Painter	2·0%	6·3%
Coalworker	0·5%	..
Chimneysweep	0·5%	..
Metal worker	..	3·2%

Lung-cancer Patients

We sought information on lung-cancer patients in respect of residence, occupation, and smoking. We were able to obtain data about 63 male and 6 female patients.

Male Cases

Of the 63 males 17 (27%) were classified as having epidermoid carcinoma, 11 (17%) as adenocarcinoma, 25 (40%) as anaplastic oat-cell carcinoma, and 10 (16%) had no histological diagnosis. Their age distribution is shown in fig. 2. In the clinically diagnosed cases the patient himself was interviewed. 53 cases had come to necropsy, and for these, all of whom had died between 1958 and 1960, the information was obtained from relatives or friends as follows: wife 52%; son or daughter 19%; aunt, uncle, niece, nephew, or in-laws 21%; and friends 8%.

Occupation and residence.—Of 61 cases where the patient's usual occupation was known, 87% were labourers and 13% were white-collar workers. This is somewhat different from the control group which contains more white-collar workers ($\chi^2 = 4{\cdot}1$, $P < 0{\cdot}05$). The cases with industrial exposure are listed in table II: there is no statistical difference between the two groups in respect of these occupations, though there is suggestive evidence of a higher lung-cancer rate for painters and metal workers which is in line with previous findings.[3]

3. Wynder, E. L., Graham, E. A. *A.M.A. Arch. industr. Hyg.* 1951, **4**, 221.

The cases of lung cancer with industrial exposure were equally distributed as to histological type. All but 1 of the male patients had resided in Venice for at least twenty years.

Smoking history.—92% of the male patients were smokers, including cigarette smokers 84%, cigarette and cigar smokers 5%, cigar and pipe smokers 2%, and cigar smokers 2%. The lung-cancer group contained significantly more smokers of over 20 cigarettes per day (41% against 14%, $\chi^2 = 20{\cdot}2$, $P < 0{\cdot}01$) than the control group table I). On the other hand, the control group contained significantly more non-smokers than the lung-cancer group (29% against 8%, $\chi^2 = 10{\cdot}5$, $P < 0{\cdot}01$). Ridit analysis [4] of the amount smoked also demonstrated a significant difference between the two groups (fig. 3). When the amount of smoking is analysed by type of lung cancer, we find no difference in the amount smoked within the four histological groups.

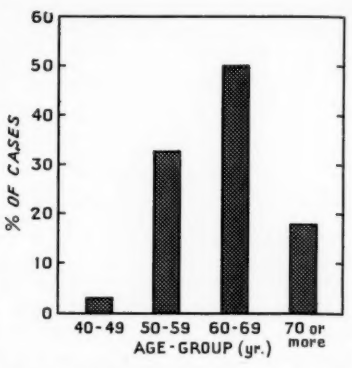

Fig. 2—Age distribution of the 63 males with lung cancer.

Female Cases

Not enough female lung-cancer patients could be interviewed to warrant statistical tabulation. The diagnoses of the 5 cases which underwent necropsy included 1 epidermoid carcinoma, 2 adenocarcinomas, and 2 oat-cell carcinomas. The 6th case was diagnosed clinically. There were 2 non-smokers among these women, both of whom had adenocarcinomas. 3 of the smokers smoked 10–20 cigarettes per day, and 1 smoked 21–34 per day; all of them inhaled. All the women had resided in Venice for at least twenty years, and none had been exposed industrially.

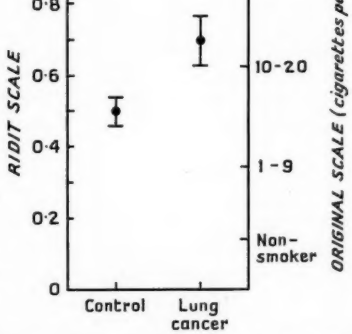

Fig. 3—Amount of smoking in Venetian males.

DISCUSSION

Motor traffic and industrial fumes are virtually absent in Venice; but in many parts of the world these are the major causes of air pollution, and many believe that air pollutants significantly influence lung cancer. Coal is used in Venice, about two-thirds of the homes being heated by coal, and the remainder by oil. Homes require heat from about November to March. There is therefore some pollution from coal burning and from motor boats; but this is relatively slight. During the winter and early spring fog is not infrequent over Venice, the mean number of foggy days being about forty. The direction of the winds is also important, particularly in relation to the nearby industrial city of Mestre. The winds

4. Bross, I. J. *Biometrics*, 1958, **14**, 18.

tend to be north-east and to a lesser extent south-east, thus not being in the direction of Venice.[5] The air in Mestre has been shown to be least polluted in the region of the harbour facing Venice.[5]

We are planning further chemical studies of air pollutants collected in Venice.

Because most Venetians have lived in Venice for over twenty years, one can study a stable population which has not been significantly exposed to general air pollution in other areas. Previous studies [6–8] have shown that the prevalence of lung cancer in Venice is as high, or even higher, than in most other Italian cities, such as Milan and Turin which are industrial centres with much motor traffic. Our findings agree with these studies. Venetian men smoke at least as much as men in other Italian cities,[2] and we found that those with lung cancer smoked considerably more than men in the control population.

The group we studied contained a smaller proportion of white-collar workers than the control group—a difference statistically significant at the 5% level. An analysis of smoking by occupation did not reveal any differences. In view of the relatively slight difference and small number of cases involved this finding is better evaluated together with more extensive studies.[3 9 10] It may not be fortuitous that certain workers, such as painters, cabinet makers, carpenters, and metal workers, appear among the lung-cancer group, although we have not studied enough cases to permit statistical evaluation of these specific occupations. All the workers in these suspected occupations were also smokers, but clearly occupational exposure must be considered in any study of environmental factors of this type. We were especially interested in the risk among glassworkers; 6 of the 63 lung-cancer patients were glassworkers, and they all smoked. But we cannot conclude on this basis that glassworkers are more liable to lung cancer in view of the relatively high number of glassworkers in the Venetian population. A more detailed study of the causes of death among this group might be helpful.

The number of adenocarcinomas in our study is higher than in the United States; this previously impressed Ferrari and Kreyberg,[11] who think it possible that, because no thoracic surgery is done in Venice, some lung-cancer patients may go to Padua for surgery. Thus a selection of cases with a better prognosis (including a number of epidermoid carcinomas) may leave Venice, so making the Venetian figures qualitatively less representative. Another likely explanation, suggested by Dr. John Berg, is that necropsy data in general show a higher proportion of glandular lung cancer because, being situated more peripherally, they are relatively less common in surgical studies.

We found no difference in smoking habits between the patients with epidermoid carcinomas and adenocarcinoma of the lung. This is at variance with other studies which suggest that heavy smoking is more prevalent among patients with epidermoid carcinoma, though few studies have included enough adenocarcinomas for adequate analysis of the problem. Further studies seem indicated, especially of the particular types of adenocarcinoma as compared to alveolar carcinomas of the lung. Our impression is that adenocarcinomas are related to exogenous factors, though less so than epithelial carcinomas, but the epithelial types are more likely in the absence of exogenous factors.

Epidemiological Considerations

Our investigation differs from most other studies of the relation of air pollution to lung cancer in a given locality, such as those of Eastcott in New Zealand [12] and Dean in South Africa,[13] in that we have investigated, as well as the specific smoking habits, the occupations of lung cancer and control patients:

Eastcott, for instance, compared only the total tobacco consumption of England and New Zealand, and he gave no details of the smoking habits of the immigrant groups. Similarly, Dean presented no data on the occupation or the smoking habits of the British immigrants and natives in South Africa. We think that such facts are necessary before one can conclude that differences in the lung-cancer death-rates between two groups are related to general air pollution, particularly if the differences are relatively small.

Our findings have certain limitations:

A precise comparison between two areas of the incidence of any cancer is not feasible without common standards of medical diagnosis and recording, and knowledge of the age distribution of the populations involved. No data are available on the age distribution of the Venetian population, but it may well be that, because of the economic situation of Venice, its population is somewhat older than that of other Italian cities. Though an exact comparison between various Italian cities may thus be misleading, lung cancer is relatively not an uncommon disease in Venice—and this is even more impressive knowing that lung cancer has a younger age-distribution than most other major cancers.

Because our information about those patients who had been dead for up to two years was obtained from relatives and friends, the facts given must be regarded with some caution. Our series contained more supposed non-smokers in the lung-cancer group (8%) than in most retrospective studies in which the patients themselves were interviewed. None of the non-smokers in the lung-cancer group were seen themselves; wives provided the information in two cases, brother or sister in two, and an in-law in the other.

The total number of cases of lung cancer is relatively small, and most of the interviews were with relatives, whereas the controls were interviewed personally; but the lung-cancer group was found to smoke more than the control group and to have fewer non-smokers—differences found significant at the 1% level.

Finally, we would emphasise that any single epidemiological study, especially involving a special population group, must be evaluated in the light of the total evidence and the degree of difference involved. Despite the limitations, when our findings are regarded as part of the total epidemiological concept of lung cancer, they clearly suggest that cigarette smoking contributes significantly to the risk of lung cancer, even when air pollution from motor vehicles and industrial sources is very slight.

SUMMARY AND CONCLUSIONS

In Venice, a city with very little air pollution from motor vehicles and industry, the male lung-cancer rate is as high as in other major Italian cities.

In the present investigation residence, occupations, and smoking habits of Venetian controls as well as Venetian lung-cancer patients have been studied.

When the findings are evaluated in the light of the total epidemiological pattern of lung cancer, they suggest that cigarette smoking is an important factor in the development of lung cancer in Venice.

We are grateful to Charlotte Zweifach for help with the tabulation and analysis of the data.

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LUNG CANCER IN ICELAND

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LUNG cancer used to be rare in Iceland. In the years 1932–50, of 1738 necropsies on people 21 years and older, only 14 showed the disease (11 males and 3 females).

In a previous paper [1] I have attributed this rarity of lung cancer to a low consumption of cigarettes: in 1924, when the population of the United Kingdom was smoking 1·73 lb. per head, the population of Iceland smoked only 0·23 lb. But, as my chart shows, Iceland has been catching up fast in the smoking race.

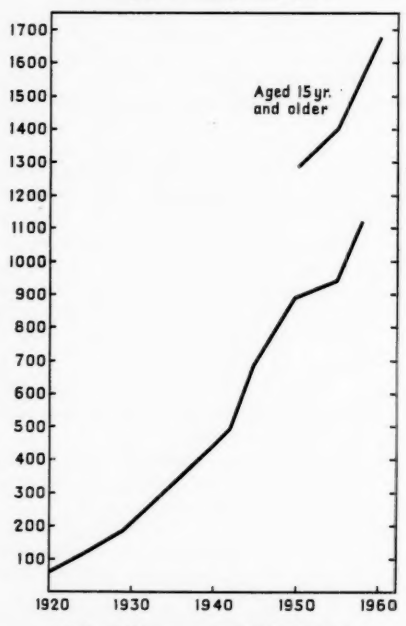
Not until the last decade did lung cancer show any considerable increase:

LUNG CANCER FOUND AT NECROPSIES IN THOSE 21 YEARS AND OLDER

Years	Males	Lung cancer	%	Females	Lung cancer	%
1932–40	356	2	0·6	288	1	0·3
1941–45	270	3	1·1	208	0	..
1946–50	392	6	1·5	224	2	0·9
1951–55	409	13	2·9	372	4	1·1
1956–60	661	19	3·0	513	12	2·3

It is noteworthy that, shortly before the rise in lung cancer took place, steps were taken to purify the air in Reykjavik, where half the population live. Until 1943 all heating in Reykjavik was derived from coal or oil, and a layer of coal smoke would be seen over the town on cold winter mornings. But in 1943–44 hot water was piped into most of the houses from hot springs outside Reykjavik, and this municipal heating system has replaced the coal and oil stoves, with the result that the air of Reykjavik is now purer than that of any capital in Europe. The increase in lung cancer cannot be attributed to smoke from fires, whether domestic or industrial.

1. Dungal, N. *Lancet*, 1950, ii, 245.



Sale of cigarettes per head (1920–59).
Number of cigarettes sold per head from tobacco monopoly. Probably 10% may be added for cigarettes from other sources.

TYPES OF LUNG CANCER

The carcinoma has been classified histologically as adenocarcinoma, 25; oat-cell carcinoma, 22; squamous-cell carcinoma, 5; undifferentiated, 5; alveolar, 3.

Of the 14 carcinomas between 1932 and 1950, 9 were adenocarcinomas. In smokers the carcinomas are mostly oat-cell or undifferentiated spheroidal-cell, with a few squamous-cell. Though we have found adenocarcinomas in smokers, in our experience the typical smoker's cancer is an oat-cell carcinoma. In many other countries squamous-cell carcinomas are common among smokers, but in Iceland smoking seems to produce a more undifferentiated and perhaps more malignant type of tumour of the oat-cell type.

The type which we call alveolar carcinoma seems to be in a class of its own. The cancer starts in one or both lungs at the same time, often with fever, and is clinically taken for a pneumonia. After several weeks its true nature becomes plain, and it may cause death in a few months. In these cases the process seems to originate in the alveolar epithelium and spreads from one alveolus to another, and from one terminal bronchiolus to another, until extensive areas of lung are consolidated. This type seems to have nothing to do with smoking, and its behaviour suggests a viral origin.

SUMMARY

Lung carcinoma was rare in Iceland until the past decade, when it has been much commoner. The increase cannot be put down to atmospheric pollution; for in Reykjavik, where most of the cases have occurred, a conduit from natural hot springs was introduced in 1943–44, since when the air has been exceptionally pure. The sale of cigarettes, on the other hand, has increased very considerably.

Toxic Chemicals in Agriculture

Protective measures now in force against toxic chemicals used in agriculture and food storage are generally successful; but further fundamental and applied research is needed. This conclusion has been reached by a research study group which was appointed by the Government early in 1960 and whose recommendations the Government intends to implement. In its report the study group states that, while the great majority of chemicals apparently do no harm to wild life, a few are dangerous, and more work needs to be done on this aspect among others.

World Health Statistics

The World Health Organisation has issued the 11th volume of *Annual Epidemiological and Vital Statistics*, which covers the year 1958.[1]

This volume includes information on the area of countries and total population by sex, general vital statistics, causes of death by sex and age, infective and parasitic diseases, health personnel, hospitals and similar establishments, prophylactic vaccination against eleven diseases, and number of physicians according to specialty. In addition, for the first time data on hospital inpatients are included; these are for the years 1955–58.

1. Annual Epidemiological and Vital Statistics 1958. Geneva: World Health Organisation. Pp. 857. £4. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

Special Articles

SHORT-STAY PSYCHIATRIC UNIT IN A GENERAL HOSPITAL

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ASSISTANT PSYCHIATRIST TO THE HOSPITAL AND THE GROUP

ONE of the many interesting changes and experiments which are being tried and discussed in the mental health services today is the proposal that mentally ill patients should not be segregated, but should become part of a "balanced hospital community" such as McKeown has proposed.[1] The research project soon to be started at Birmingham will, it is hoped, show how feasible this will be, and the time may come when all patients who are now treated in mental hospitals will be treated in a general hospital. But a change of this kind would not be simple, and we feel that there is room for some intermediate scheme—one that, though it increasingly shifts the emphasis of psychiatric treatment towards the general hospital, will yet support and use the services of the mental hospital. An arrangement of this kind is already being tried at the psychiatric unit of The West Hill Hospital, Dartford, and Bexley Hospital, a large neighbouring mental hospital.

THE ARRANGEMENTS

The Unit

The unit is run on the open-door principle. It has 56 beds (33 for women and 23 for men). It is staffed by 1 senior house-officer, 4 sisters and 22 nurses (male and female). Student nurses from the general wards are allocated to the unit and take an active part in physical, psychological, and social therapy. Outpatient, inpatient, and day-patient services are provided—the latter as part of the inpatient unit.

Thus all forms of treatment, backed by such general-hospital departments as social service, occupational therapy, and anæsthetics, are available at one centre. The small size of the department means that it is a compact and intimate community. The patient is more readily persuaded to accept early treatment in a general hospital. Considerable emphasis is placed on group participation, including occupational therapy, and the use of a mixed nursing staff has improved the ward atmosphere, especially for men patients. Some of the student nurses who have worked in the unit have decided to take further psychiatric training after they qualify.

The Hospital

Junior medical staff from Bexley Hospital, as well as the senior psychologist there, help at outpatient clinics. For some time each consultant at Bexley has been responsible for direct admissions from an agreed part of the total catchment area of the hospital. This was fairly easy to arrange because each consultant already held outpatient clinics in a different general hospital and could normally be responsible for the patients living near that hospital—though the general practitioner and the patient still, of course, had freedom of choice of consultant and hospital. In this way one of us (H. S. C.) is responsible for the area round West Hill Hospital; and, thanks to the close connection between the general hospital and the mental hospital, no administrative difficulties in transferring patients have arisen. In our view, medium and long-stay patients need a milieu where the emphasis is on rehabilitation and they are therefore transferred from the short-term unit to Bexley or elsewhere.

The West Hill unit provides extra teaching material for undergraduate and postgraduate students who come to Bexley Hospital for part of their clinical training.

THE PATIENTS

Since 1951, the number of admissions to the unit has trebled, and it is now approaching 600 a year. In 1957, when voluntary patients were first admitted, they were 44% of all admissions, but by 1960 they were 69%, partly because of the greater willingness of the patient to accept treatment in a general hospital.

Of the 588 patients admitted to the unit in 1960, 138 came from other areas and 450 from our own catchment area. Of these 450, 54 were transferred to Bexley Hospital (which also admitted 228 directly) and 12 to another local mental hospital (which also admitted 34 directly), because they were regarded as potentially long-stay patients. Between them, in 1960, the three hospitals admitted a total of 712 from the area. This gives a crude annual admission-rate of 2·69 per 1000 population, which is higher than the national average of 2·16 for 1959.

In the unit the average number of beds occupied was 48 in 1953. By 1956, when all the beds were acute, it fell to 31; when voluntary patients were admitted in 1957, it rose to 32; and with the admission of day-patients last year it rose further to 35.

Our impression is that the development of psychiatric units in general hospitals may of itself lead to an increase in the admission-rate. Our average bed-occupation clearly reflects the evolution of the unit from a closed observation ward with a predominantly chronic population to a short-stay unit with a rapid turnover. We expect that the admission of day patients will now release more beds, for many patients do not need full admission and others, after a period as inpatients, are happier attending as day patients. This reduces the length of stay without giving rise to a sense of hurry in treatment.

In the first half of 1961 the number of day patients was 100. This was twice as many as in the previous six months and it is likely to increase further.

The number of new patients seen each year in outpatient clinics is about 300. Subsequent attendances have risen from 696 in 1950 to 2275 in 1960 and will rise further as follow-up clinics are started for discharged inpatients. Clearly more psychiatrists will be needed, but meanwhile it would seem reasonable to avoid competition for staff between the mental hospital and the general-hospital units by linking them as closely as possible.

All types of psychiatric illness are dealt with in the unit. Affective disorders predominate in the voluntary group (53%) and schizophrenia among the compulsory admissions (45%). We have not found it necessary to provide separate accommodation for the better-preserved patient. A ward divided into sections, all of which communicate, together with side-rooms, allows patients to be graded according to their stage of recovery. In our

1. McKeown, T. *Lancet*, 1958, i, 701; *ibid.* 1961, i, 1212.

experience even the very disturbed patient soon settles and is able to join the rest of the group, and we have had no difficulty in keeping our patients interested within the department. Daily visiting and weekend leave keep them in touch with their families and, as their stay is relatively short, they do not find the regime irksome. We have not found acute schizophrenia a difficult problem since, with modern therapeutic aids, even patients who have been ill for several years do not show the degeneration formerly characteristic of the disease. Wherever possible we have treated patients with neurosis as outpatients or as day patients.

As there is a large obstetrics department in the hospital we receive quite a number of patients with puerperal psychosis (4% of our voluntary cases). For some time now we have admitted the mother with her baby to a side-room, a procedure rarely possible in large mental hospitals. Other patients are noticeably helpful and considerate. A small day-nursery unit attached to the department would expedite the treatment of mothers with young children and should not be difficult to arrange in a general hospital.

Day patients seem to provide social stimulation for inpatients. Reluctant patients may be introduced to the unit in this way and persuaded to accept inpatient treatment.

The percentage of the three main diagnostic groups transferred from the unit to Bexley Hospital in 1960 was surprisingly similar—9·4% were affective disorders, 8·4% schizophrenics, and 8·1% organic mental states. This suggests the need to re-examine our views on prognosis and on the types of patient suitable for short-stay units.

DURATION OF STAY

The change from observation to treatment has lengthened the patient's stay but, except in emergency, only those thought likely to be short-stay patients are admitted to the unit. Within ten weeks most patients recover or improve enough to return home, though some may continue treatment as day patients for a short time.

Of the 282 patients admitted to Bexley Hospital in 1960 (under the care of H. S. C.) 67·4% proved to be short-stay patients (using the same criterion of ten weeks) and could have been treated at the West Hill unit, while 32·6% were medium or long-stay patients. A review of this medium and long-stay group in June, 1961, showed that 19·7% had died, 57·3% were discharged, and a further 19% had improved sufficiently to be cared for in a geriatric ward or in the community, leaving 4% still needing psychiatric treatment.

These findings suggest that only a small proportion of patients need to be transferred to a long-stay unit. If there was better provision for the elderly, a new long-stay psychiatric group would be unlikely to accumulate.

Predictions for future needs, based mainly on mental-hospital admissions, suggest that 340 short-stay beds and 500–600 medium-stay beds will be needed for a standard population of 1 million.[2] This estimate may prove to be rather too high once treatment in general-hospital units with their more rapid turnover is widely available.

DISCUSSION

On the basis of cost the small unit (say, 60 beds) may have much to commend it and a general hospital is less likely to make space for a larger one. A unit of this size would favour the "firm system" as commended by the Platt report. One of McKeown's criteria for the "comprehensive hospital" is "classification of patients strictly according to need". Treating short-stay patients in the same unit as long-stay patients—however they are separated—would not meet this eminently reasonable suggestion. Nothing produces more uneasiness and sad foreboding in the newly admitted patient than seeing others who have been in hospital for months or years.

To build large comprehensive psychiatric units, except as centres for research, will perpetuate many of the defects of the old hospital and will not provide really suitable accommodation for either the short-stay or the long-stay patient. What we need are small active units, fully integrated with a general hospital, with ready access to comprehensive schemes of community care and rehabilitation. Only in this way can we hope to remove the stigma of mental illness, encourage interdisciplinary research, and bring psychiatry into the general stream of medicine where it properly belongs.

CONCLUSION

In our psychiatric unit all patients (whether informal or compulsory) are treated in open-ward conditions in a general hospital and a day hospital is an integral part of the unit. We believe that similar units could take care of at least 80% of all psychiatric admissions to hospital.

All types of mental disorder can be treated in a general hospital setting, which the patient usually prefers. The only criterion for admission we have applied, except in emergency, is that we do not take patients into the unit if it seems likely that they will need to stay more than ten weeks.

A 56-bed short-stay unit can comfortably deal with about 600 admissions annually, if it has enough staff and access to beds in a long-stay unit. The two types of unit should, wherever possible, be under the charge of the same consultant, and they should have a distinct catchment area so that continuity of treatment may be ensured.

We would like to thank Dr. D. M. Leiberman and Dr. D. Bannister for their helpful comments.

2. Tooth, G. C., Brooke, E. M. *Lancet*, 1961, i, 710; Cross, K. W., Yates, J. *ibid*, p. 989.

The Wider World

MEDICAL ADMINISTRATION IN RUSSIA

Some Recent Impressions *

WESTERNERS think of the U.S.S.R. as consisting of large bureaucratic organisations doing vast quantities of paper work. This idea is supported by the Soviet Press itself, which often publishes complaints about too many bureaucrats and too much red tape. But, as one of a group who paid a brief visit to Russia last August, I was repeatedly surprised to find that Soviet Government agencies had fewer persons and smaller buildings than their counterparts in the West. For example, the Ministry of Health of the Ukraine has only two hundred employees in administrative, clerical, and maintenance work; the

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department of health of the State of California would be much larger. In research institutes and hospitals, fewer persons and fewer man-hours seem to be devoted to administration than in America, and possibly fewer than in Europe. Paper work is also much less than I had expected: often there was little evidence of typewriters, file cabinets, carbon copies, reports, memoranda, notes, desk calculators, and the other clerical paraphernalia familiar in the West. Instead, many records are kept in pen-and-ink in single copies, and much communication is by face-to-face visits. The Soviet Press and some Western analysts have said that Soviet doctors are excessively burdened with paper, but medical records seemed much more brief than those in the West.

It is quite puzzling how they operate with so few personnel and with so few documents. One might expect that they would need more of both, for various reasons. For example, both office clerks and physicians seem to do their paper work more slowly than their Western counterparts, and they may work shorter hours. Again, the high degree of specialisation, particularly in administrative agencies, restricts the range of the bureaucrat and clerk.

One possible explanation of the unexpected simplicity of Soviet medical administration is that Soviet agencies and medical organisations may each perform fewer tasks. As parts of larger bureaucratic systems, they are relieved of the work needed to preserve their own organisational existence—e.g., fund-raising and recruitment of staff. Soviet agencies may bombard their field personnel with fewer directives than Westerners think, and therefore the operating personnel may have more autonomy than we imagine. Again, Soviet executives may make decisions on much less information than is usual for Western executives.

The relatively small amount of administration may have a number of unintended consequences. The low development of written communication, the reliance on personal memory and personal communication (by visits and phone calls), and the shortage of skilled clerical personnel apparently produce many errors of communication and of information retrieval. Inefficient communication and errors may also lead to a great deal of unintended diversity in the Soviet medical system. Outlying areas may do things differently from the model that everyone is supposed to follow, because somehow the outlying areas never understood the messages correctly and because the centre never got clear reports about performance.

I was surprised by a number of trends that are making the Soviet health system—and indeed much of the Soviet Government—much more like the West than we suppose. The Soviet Government seems to have undergone considerable decentralisation in recent years. In many fields the All-Union Ministry of Health and the republic Ministries of Health lay down general policies, but the field personnel have considerable discretion. Higher agencies in health do not issue major policy directives until they have received the recommendations of the operating personnel. As field operations become more complex, and as field personnel become more expert and more self-confident, the decentralising trend will doubtless accelerate.

Another such Western-style trend is the growth of committees. We often think of the Soviet system as a hierarchy of authoritarian individuals, and so it was under Stalin. But of late years in health there has been a steady growth of decision-making by committees of administrators. In health affairs, leading physicians are usually members of these standing committees. Both in medicine and in education, decision-making by committees has gradually spread through the country, and it is Khrushchev's policy to encourage the same development in other kinds of work.

On technical subjects, such as health, the administrator shows growing deference to the expert who is doing the actual work. This is yet another of the unexpected Western-type trends I saw. In many agencies in health, the individual administrator or the committee of administrators regularly consults with medical leaders, either as individuals or in standing advisory committees. There may be an increasing tendency to call for social research and administrative experiments before an administrative decision is taken in the sphere of health organisation. When ascertaining whether subordinate agencies are fulfilling plans properly or are committing certain reported violations, the full-time administrators in the Ukrainian Ministry of Health do not send out one of their own staff but instead send out investigators from among the practising clinicians or scientists in the Ukrainian Academy of Medical Sciences. In deciding what types of clinical medical research to promote and subsidise, the administrators in the Ministries seem to be deferring increasingly to the judgments of the clinicians and the scientists. As Soviet techniques become more complex, and as the technical experts become more demonstrably successful in producing results, the Government administrator and the Party member will probably show more and more deference to the professional.

This is only a guess, based on very scanty evidence; but it is possible that in the field of health the Government is becoming more powerful relative to the Communist Party. Once clearly the Soviet Government apparatus was subordinate, and success was achieved primarily through a Party career. In many other areas of Soviet affairs the Party remains dominant; and it remains important in health, of course; but possibly in this field Government agencies may be furnishing more opportunities for success and self-gratification, and health personnel who are both officials and Party members may be devoting an increasing proportion of their attention to their Government duties. In health, and possibly elsewhere too, plans and operating decisions are increasingly initiated by the Government agencies themselves, with the Party restricted to the role of overseer, ensuring that the overall interests of the Soviet Union are not forgotten in the narrower work of the individual Ministry.

Since the death of Stalin, the Communist Party seems to have declined in its power within the medical schools. Under Stalin, the professor of historical materialism had a great deal of power over the curriculum and over the personnel in the medical school. He was usually considered the Party's representative within the medical school, and often he was strictly a Party careerist, without a university education. Often he was more powerful than the director, with power to expel ideologically suspect faculty members and students. Much of the medical student's time was spent listening to his lectures on Marxist ideology and Soviet history. Apparently a

good deal of resentment built up among the professional staffs.

In recent years, the power of this professor has diminished. The amount of time devoted to his courses has been reduced, and there have been attempts to make his lectures less propagandist. He is now, whenever possible, a person with both a university education and graduate training in philosophy, and much of his teaching is said to concern the history of philosophy. He is still supposed to be the ideological watchdog of the medical institute, with the right to question ideologically suspect faculty members and with the right to listen to their lectures; but power to remove or rebuke another faculty member for ideological error is now lodged in a committee of the institute. The professor of philosophy is a member of the committee, and apparently his influence is still considerable in such ideological questions; but discipline may be becoming more of a matter for group decisions, with doctors holding the majority of the votes.

One of the other post-Stalin changes is the attempt to make medical education a training for the exercise of medical judgment. In general, the entire Soviet educational system is trying to get away from the rote learning that characterised it under Stalin. This rote learning had been widely criticised in medical education. Now it is recognised that a doctor must be able to interview, and diagnose patients' social-emotional needs; and it is realised that the medical student must be able to think imaginatively and critically. Therefore, the Ministry of Health in recent years has asked teachers in medical institutes to rely less on canned lectures, give more imaginative lectures based on reviews of the current scientific periodical literature, encourage group discussion, and tolerate critical debate among students. Apparently these changes caused discontent and some resignations among the Old Guard professors who had been giving the same lectures for years. Probably some time will elapse before the old habits change completely.

As to whether the trade unions are regaining some of the functions and independence that they lost under Stalin, I am not sure. Local chapters of the Medical Workers Union may be becoming more active in the discussion of wages, working conditions, assignment of work shifts, discharges, and grievances. Like other trade unions the Medical Workers Union has in recent years been given title to a number of sanatoria, vacation camps, and other recreational facilities; the local chapters manage them and decide which employees and family members will go.

Children seem to be a favoured class generally in the U.S.S.R.: in many ways they seem to be served better than adults. We could not find out for sure, but it is possible that the long-established Soviet distinction between pædiatric and adult medical services may now be used to allocate somewhat better facilities and personnel to pædiatric medical care. If such a difference exists, it might be deliberate or it might simply be unplanned—as is so much of the supposedly planned Soviet system.

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Conferences

PSYCHIATRY IN AFRICA

THE First Pan-African Psychiatric Conference was held at Aro Hospital, Abeokuta, Nigeria, from Nov. 12 to 18. Convened by Dr. T. Adeoye Lambo, medical superintendent of Aro Hospital, it was attended by doctors, nurses, and social workers from many African countries, including the Union of South Africa, and also from Mauritius, Western Europe, the United States, and Canada. The subjects discussed included nutrition, the incidence of general and neurological diseases, the distinctive features of psychiatry in Africa, the stresses resulting from the interplay of the indigenous and Western cultures, and the work of the native practitioner of medicine. Members of the conference had the opportunity of meeting the Prime Minister of Nigeria, Sir Abubakar Tafawa Balewa, other Federal and regional Ministers, and the local paramount chief, the Alake of Abeokuta. The Federal Minister of Health, Dr. M. A. Majekodunmi, presided at the opening ceremony.

The inaugural address was given by Sir AUBREY LEWIS (London), who brought greetings from W.H.O. He pointed out that psychiatry was universally applicable since there was no fundamental personality difference between different ethnic groups. He touched on the role of the native practitioner and stressed the need for more universities and for the maintenance of high standards and the importance of the social sciences, especially demography and genetics. He urged African psychiatrists to pitch their standards high.

Juvenile Delinquency in Europe and Africa

Lady LEWIS (London), opening a discussion on juvenile delinquency, pointed out that, since disruption of the parent-child relationship is an important cause of delinquency and the delinquent is likely to be an unsatisfactory parent, the disorder is often self-perpetuating. Adaptive or socialised delinquency could arise when parents were over-indulgent or preoccupied with their own work, and neurotic children were often the reaction to anxious parents. Brain damage as a cause of delinquency should be borne in mind. Family guidance was a signal need, and a problem was how to reach families which did not apply for help.

Dr. PETER SCOTT (London) said that the prevention of delinquency was still largely empirical, and must ultimately depend on social measures and provisions, especially education, including that of parents. He contrasted delinquency caused by poverty of resources with that associated with over-satisfaction of needs, and stressed the importance of critical periods of child development. Social disturbances when a child was 4–5 years old seemed particularly significant. A child might need to escape from its parents—hence the value of day nurseries. The prevention of recidivism called for the cooperation of psychiatrists and psychologists with the staff of remedial units. There was a need for well-run hostels and for research into effects of remedial measures, including detention.

Dr. T. ASUNI (Abeokuta) discussed some aspects of children's problems in Western Nigeria. Bed-wetting was tolerated up to the age of 7, and in any case caused little inconvenience. Hysterical fainting was a common reaction to stress. Mental subnormality was not a serious problem, owing partly to the high infant-mortality rate; and mongolism was rare. There was need for more study of delinquency in relation to varieties of cultural pattern.

Dr. A. C. RAMAN (Mauritius) discussed the incidence of mental illness in the oldest male children in different sects and

the labouring classes in Mauritius. He had found this to be affected by cultural differences in the status of the oldest male child.

Dr. TIGANI EL MAHI (Khartoum) pointed out that delinquency was ultimately defined by law, and was sometimes permitted at certain festivals. A change in the law would change the incidence of delinquency. He contrasted the greater stability of the mores of a tribal society with those of a society whose basis was mainly geographical. Many social problems were created by the loss of old social values before new ones were acquired. Polygamy had at one time had a biological value and been readily accepted. Indeed a wife had been known to apply for a divorce because her husband refused to marry a second.

Cultural Factors in Child Development

Dr. LAMBO (Abeokuta) discussed the influence upon Nigerian children of the distinctive features of the national culture. The fact that the child is carried on the back of the mother gave it a strong sense of security, and polygamy created an extended family system. Children were often breast-fed until the age of 2, and during breast-feeding there was a taboo on sexual intercourse; hence, on weaning, the child was physically displaced from the mother's bed by the father. Nevertheless, Dr. Lambo had failed to trace neurotic behaviour to any stresses in childhood, which on the whole was happy and hampered by singularly few restrictions, and there was no toilet training. Ridicule was a potent social control. In a large polygamous family the paternal grandfather was the authority, and the child on weaning lived with the grandparents, and with numerous uncles and aunts. He wondered whether the characteristic optimism and the self-assurance of the Nigerian might not be due to the oral-erotic satisfaction of prolonged breast-feeding. He interpreted circumcision at puberty as an attempt to promote personal integration, to shift libido to adult values and enhance the distinction between the child and the adult. How far it succeeded was another matter. Since there was no attempt to conceal parental sexual intercourse, sex education was a matter of course, and masturbation was acceptable.

Malnutrition

Dr. ROBERT COLLIS (Ibadan) stressed the mental symptoms of protein malnutrition in kwashiorkor, regarding them as more than merely the child's reaction to its discomfort. A survey of four villages in Western Nigeria had shown that the diet contained insufficient protein in all and not enough calories in three. Most inhabitants acted as host for four different parasites. Between the ages of 2 and 3, children in the Nigerian villages were $7^1/_2$ in. shorter than the children of the university staff. There seemed to be a correlation between diet, emotional state, and physical activity.

Dr. J. C. EDOZIEN (Ibadan) discussed the importance of diet in relation to psychological adaptation to change and reactions to disease in later life.

In the adult African the mean level of 17-ketosteroids was 4 mg. per 100 ml. lower than that of Europeans. It was not known whether this difference, which is nutritional in origin, affected emotion and, in particular, sexual behaviour. The serum-cholesterol in Nigerians was 75 mg. per 100 ml. at birth, and for some years it remained lower than in Europeans. In adult Nigerians the blood-cholesterol level was correlated with income, and in the higher-income groups reached the European level. In ten years there had been only 6 cases of coronary thrombosis in Nigerians in University College Hospital, Ibadan. One might speculate whether the level of blood-cholesterol during the first years of life might not be a significant factor in relation to the liability to develop atheroma much later.

Neurology in Nigeria

Sir RUSSELL BRAIN (London) gave a lecture on modern trends in neurology and neurological research, and stressed the importance of geographical neurology, and the study of genetic, nutritional, infective, and environmental factors in relation to the local incidence of nervous disease.

Dr. J. L. MONEKOSSO (Ibadan) spoke on tropical endemic neuropathies with particular reference to a syndrome the precise cause of which was still unknown. Lesions of the optic and auditory nerves and laryngeal palsies might coincide with lesions of the spinal cord, posterior nerve-roots, and peripheral nerves, causing paraplegic, ataxic, and polyneuritic syndromes. There was a high blood-pyruvate level, and, if treatment with mixed vitamins was begun early, the prognosis was good. The cause was to be sought in dietary deficiency. Dr. Monekoso stressed the frequency of subclinical cases of the tropical neuropathies.

Dr. S. C. KAUSHIK (Ibadan), speaking on patterns of neurological disease, drew attention to the high incidence of meningitis and cerebrovascular disease with or without hypertension.

Dr. A. O. LUCAS (Ibadan) reviewed the various forms of meningitis, and particularly pneumococcal meningitis—a disease with a high incidence and a positive correlation with pregnancy. The mortality was 29 out of 66 cases; and the sequelæ, such as mental deterioration, hemiplegia, and deafness were often severe in the survivors.

Dr. A. PIRAUX (Marcinelle, Belgium) discussed epilepsy in Central Africa. Of 209 cases there was a family history in only 17%. 30% constituted social problems, and there was a high correlation between epilepsy and acts of violence.

Psychiatry in Africa

Members of the conference visited Aro village about a mile from the hospital, where patients with mental disorders are boarded with the villagers, the village chief himself taking 5. All patients have relatives with them and attend the hospital daily for treatment. They may stay in the village for up to six months.

Prof. A. LEIGHTON (New York) described the Cornell-Aro Epidemiological Study—a joint project of Cornell University and Aro Hospital—which is carrying out a survey of mental illness in Western Nigeria.

Dr. C. HUGHES (New York) described the pattern of social disintegration in some villages and said that there was a higher incidence of mental disorder in the disintegrated than in the integrated villages.

Dr. ROBERT COLLIS, Jr. (Abeokuta) considered possible correlations between physical and psychological disorders, and Prof. O. ODEGARD (Oslo) those between different types of social organisation and types of psychoses. A competitive society, he said, tended to produce paranoia. While personal conflicts were important causes of mental disorder, conflicts between one society and another seemed to be cohesive within a society and to diminish individual neurotic symptoms.

Dr. T. ASUNI (Abeokuta) said that the suicide-rate in Western Nigeria was very low—less than one per 100,000—being higher among Christians and Pagans than among Moslems. Traditional respect for elders and the high level of family care helped to keep the suicide-rate down.

Dr. HENRI COLLOMB (Dakar) said that the incidence of depressive states in a mental hospital in Dakar was the same as in Europe, but suicide was rare. Self-reproach and guilt feelings characteristic of European melancholia were not found in Africans, perhaps because they did not have the same sense of the structure of time and the significance of the past.

Dr. V. R. NTSEKHE (Basutoland) spoke of the bad effects of superstition, witchcraft, sorcery, and some aspects of ancestor worship; a major psychological stress might be created and perpetuated by the native healer. Moreover, since the patient expected the native healer to divine his symptoms, he thought it unnecessary to give a history to the doctor.

Dr. TIGANI EL MAHI (Khartoum), reviewing future orientation of mental health in Africa, said that in African culture

medicine, magic, and religion could not be separated. Some depressives were to be found in monasteries, and some witches were involutional melancholics. In the Sudan native medicine had a long tradition and a considerable intellectual content. The native practitioner dealt with psychological illness by means of hypnosis, psychodrama, a form of psychoanalysis, and the induction of mystical states and ecstasy. One must distinguish between tension and neurosis. In the conflict of cultures it was natural that there should be tensions, but, as had been said, " it is not normal to be normal in abnormal conditions ".

The proceedings of the conference are to be published in the *West African Medical Journal*.

GENETICS IN MEDICINE

A SYMPOSIUM was held on Dec. 1 by the Royal College of Physicians of Edinburgh, under the presidency of Dr. J. D. S. CAMERON, in which the speakers were drawn from the staff of the M.R.C. Clinical Effects of Radiation Unit at the Western General Hospital, Edinburgh.

At this meeting Dr. W. M. COURT BROWN gave a Freeland Barbour lecture on Cytogenetics in Medicine. Dealing first with abnormalities present from conception, he estimated that mongolism (by far the commonest autosomal abnormality) occurs once in about 700 births. A survey, in which he is engaged, of the sexing of all babies born in the hospitals of a large part of southern Scotland, shows abnormalities of the sex chromosomes in 1 in 450 babies born. From this he estimated that about 1900 babies were born with sex abnormalities in Great Britain each year.

Discussing the extraordinary sex-determining power of the Y chromosome, he said that even XXXXY individuals were phenotypically male (or nearly so). Commenting on the clinical usefulness of cytogenetic studies, Dr. Court Brown pointed out that 40% of patients with primary amenorrhœa have some chromosomal abnormality. He went on to show how chromosome studies had contributed to genetic mapping. XO populations had an unusual prevalence of sex-linked recessive defects. Individuals with Turner's syndrome having XO constitution, a deletion on the short arm of the X chromosome, or long-arm isochromosomes all had a very short stature, while those with a deletion on the long arm of the X chromosomes had normal stature. This suggested that an X-linked recessive gene or genes, which resided in the short arm, had a major effect on stature.

Turning to abnormalities originating in somatic-cell chromosomes, he remarked that there was evidence from the irradiation of patients with ankylosing spondylitis that the incidence of leukæmia increased with dose. He suggested that governments should assume a simple proportional relationship between dose and incidence, with no threshold. Examination of irradiated tissues showed all possible kinds of chromosome abnormalities. That the proportion of aberrant cells rose after irradiation had ceased was a puzzling discovery. One man had 20% of abnormal blood-cells as much as thirteen years after therapeutic irradiation. This might explain some of the long latent periods in cancer production. Cancer production was seen in two phases—initiation and promotion. For example, urethane appeared to be a powerful initiator of some subthreshold neoplastic states, while cigarette-smoking promoted cancer in the lungs of already susceptible individuals.

Dr. Court Brown concluded by describing the abnormality of autosome 21 in which the long arm is deleted—the so-called Philadelphia chromosome, found in chronic myelogenous leukæmia. He showed how cytological studies can help us to follow what is going on in the tumour, and how the cytology of chronic leukæmia becomes more variable as the neoplastic process ages. New cell lines developed and died out and were replaced by others until one line was successful and reproduced so rapidly that it brought about an acute leukæmia that led to the death of the host—a sort of evolutionary microcosm.

In England Now

A Running Commentary by Peripatetic Correspondents

I WAS short-listed again last week. Out from the back of the wardrobe came The Grey Suit for inspection and rehabilitation. While I was rubbing away with ' Kleenit ' at a spot of unknown ætiology over the left knee, I began thinking about The Suit. A rapid review (mental) of the literature showed that previous references on the subject were scanty. Here, obviously, was the thesis for the paper one always feels one should be writing instead of exchanging anti-consultant recriminations in the saloon bar.

Title? How about " The Suit and I "? Or, " Clothes and the Candidate, the Natural History of The Grey Suit "? As there has only been one Grey Suit in my postgraduate life the review of case-histories would be simple. A series of one—brand new for the M.B., gleaming in its pristine freshness, its 22in. bottoms the dernier cri in Queen Square—progressive decline to obsolescence through multiple primaries and multiple finals—change of behaviour pattern to repeated attendances at appointment interviews, by now bell-bottomed and wasp-waisted. This would be just the introduction; the meat of the paper would be in the Management of the Senile Suit. The pros and cons of the two orthodox alternatives would be discussed; the shabby-genteel or the flagrantly-impoverished treatment. I'm a shabby-genteel man myself—a kind of Alfred Jingle of the interview rooms. Before each interview The Suit is cleaned, pressed, and generally serviced. After each it is deserviced with beer and cigarette ash. Judging by results, this is not particulary effective. Perhaps next time I might try the frayed cuffs, holes-in-elbows approach.

The paradox, of course, lies in the prognosis. Successful treatment terminates the effective life of The Suit. It becomes a cocoon from which a chrysalis consultant emerges in The New Blue with narrow lapels. On the other hand, if treatment is unsuccessful life is indefinitely prolonged. The symbiosis of Clothes and Candidate goes on and on, and is ended only by the departure of the host into general practice or radiology.

* * *

LONDON FLAT. Pleasant and comfortable 2-bedroom, self-contained. Occupier going overseas about Christmas. Near Kings Cross College Hospital. 5 miles Charing Cross and R.C.S. 7½ gns. per week.

At last *Pulse's* advertisement has given recognition to the alma mater of us peripatetic correspondents.

* * *

It was an undertaking to conduct half a hundred doctors with their wives on a study tour of Israel; but I felt fairly confident, for I had rubbed up my schoolboy Biblical Hebrew and taken lessons in modern pronunciation and usage. For the first few days we were invariably greeted in impeccable English, but I grasped my opportunity with two chubby and grubby urchins, aged six and four, whom I met in the back streets of Jaffa. In a dignified and suitably patronising manner I addressed them in my most fluent Hebrew. Before I had finished they broke in with a devastating, " Chuck it, mister, we speak English." This was disconcerting, but perhaps merely unlucky. On my return to the hotel I spoke in even more polished phrases to the chambermaid. A charming smile of recognition spread over her features. " Mais, monsieur," she purred, " Moi aussi, je parle français." " Never mind," said my wife, consolingly, " She at least didn't take you for an Englishman."

* * *

Shades of Pilkington once again,
The B.M.A. blacklist was all in vain.
For in this small East Anglian town,
Home of the bicycle and the gown
And the super intelligent licensed clown,
The humanists tread the doctors down.

Letters to the Editor

HEATING-VENTILATING-COOLING

SIR,—In his letter of Nov. 4 Professor Wells asks that greater priority be accorded to " amelioration " of the operating-theatre environment and for more guidance from the medical profession to the engineers and others concerned with heating, ventilating, and air-conditioning hospital wards and operating suites. His views support the plea made by Prof. D. M. Douglas at the St. Andrews conference on the Design of Hospitals and Medical Schools,[1] that " the needs and safety of the patient as a whole and the comfort of the staff working as a team " be given consideration as well as the need to keep the theatre air clear of pathogenic organisms. It is thus logical to ask whether enough is known of the needs of the unconscious patient and his responses to the operating-theatre environment to support sufficiently comprehensive recommendations?

You have permitted me (Sept. 23) to reiterate a suggestion submitted to the Royal College of Surgeons of England nearly ten years ago that there was need for more detailed studies than had been made hitherto of the thermal environment of surgical teams and their patients, and you allowed me to direct attention to the need for identifying with some precision the levels of warmth which are potentially dangerous in Great Britain for the unconscious individual on the operating table and for early recognition of the hazard to which he is exposed when these levels are exceeded. Studies to provide this information would also point to optimum requirements for the patient from which the design criteria for the theatre architect and, later, the standard operating procedures of the theatre engineer could be derived. Without this information both the design and operation of refrigeration systems may prove uneconomic and inefficient, and as Mr. Ian Leslie remarks in *The Lancet* of Nov. 11 " . . . no hospital can be better than the brief that is given to the architect ". Techniques are available today for recording in the theatre, or telemetering remotely, the body-temperature, the heart-rate, the respirations, &c., which were not to hand 10 or 20 years ago, and so are technicians who can use them.

The information to be gained would not only provide design criteria; it would give the surgeon additional knowledge concerning his patient's welfare and permit a factual appreciation of the physiological responses of the unconscious man, woman, or child under operating-theatre conditions when exposed to environmental warmth of varying degree. There would also be valuable byproducts. For example, further light might be thrown on the contraindications to atropine when the sweating mechanism is likely to be invoked by unavoidable warmth, to which Dr. Hoyle and Dr. Strach (Nov. 4, p. 1042) directed attention.

A useful start might be to establish for British summer and winter conditions information similar to that provided in America by Clark et al.[2], who showed that when the wet-bulb temperature in the operating-theatre exceeded 75°F in New York the patient's body temperature began to rise. The identification of the levels at which it begins to fall will provide useful data bearing directly on optimum criteria. Unfortunately the unconscious patient cannot say whether he is " comfortably warm " or " comfortably cool ", which prevents the use of a comfort index, probably the most useful tool for defining desirable levels of environmental warmth for domestic and industrial communities (except where heavy work is entailed).

Although, Sir, there has been a healthy interest in recent years in climatic physiology, stemming largely from the need to evaluate and " ameliorate " a variety of operational situations encountered in World War II and coordinated in Britain by the Medical Research Council's climatic physiology committee, little interest has been shown either by the surgeons or the physicians, in what, for want of a better term at the moment, one might call " clinical climatology ". It is little wonder that, when answering a question concerned with the need for improving conditions in operating-theatres, the Minister of Health informed Sir Samuel Storey that he had not decided on the timing of improvements, for it is doubtful whether the medical profession is in a position to define with confidence and precision some of the criteria such improvements should be designed to satisfy.[3] Is not this one of the reasons why progress in this area has been so sluggish?

I wonder, Sir, whether Professor Wells would be willing to amplify his remarks to indicate the practical steps he considers might be taken now by the profession to assist in the " amelioration " of the conditions to which he refers in his final paragraph.

Office of the British Navy Staff,
Washington D.C., U.S.A. F. P. ELLIS.

*** Surgeon Captain Ellis sent a copy of his letter to Professor Wells, whose reply follows.—ED.L.

SIR,—You kindly allowed me to see all this correspondence so that I may attempt a reply at this stage. I am grateful to all those who have so far contributed their quota of fact and opinion and I have made several attempts to cope with the problem you have set me—unsuccessfully. I do not believe anyone is, or could be, equal to this task, because we are all a bit shaky on our facts and we have not sufficiently pooled our opinions.

Mr. Constable (Nov. 25) doubts whether ducts get dirty. In Liverpool we know to our cost and sorrow that they do. Dr. Blowers (Dec. 9) defends his faith in the piston effect, but (necessarily in a short letter) glosses over the attendant difficulties such as are introduced by the circulation of nurses and others between the theatre and ancillary rooms. My local consultant tells me that he can, for £500, add a cooling unit to a £3000 ventilating plant. Mr. Constable says (in effect) that the running cost for such a cooling unit is £50 a year. If these be true facts, what is all the fuss about?

In my letter of Nov. 4, I intended the use of small package-units, one in each operating-room, to provide, under local control, cooling by recirculation without filtration, on the relatively few very hot days of the year. Mr. Constable in his comments on this suggestion is really discussing something quite different.

Dr. Blowers and Miss Crew delicately remind us that staphylococci are spread from the " lower parts of the body " of theatre personnel. More rational dress might solve that problem more cheaply than downward displacement, and thirty years ago we saw theatres in Holland where a thin film of water was kept on the theatre floor throughout the day, to cope with this hazard.

Surgeon Captain Ellis, in his admirable communication, traces the abortive history of these problems and reminds us that the Minister of Health " is doubtful if the medical profession is in a position to define . . . the criteria " which current improvements should be designed to satisfy.

Finally, Surgeon Captain Ellis asks me what I suggest we should do about it. Already we have begun a study of temperature changes in patients on the operating-table, but this is only a local effort. I think there is no doubt that what we need is more general discussion and experiment. In my experience a working party representing all the disciplines and skills is ideally suited to a task of this character. Arising on the discussion that takes place around the table various members of the party undertake appropriate investigations which are brought

1. See *Lancet*, July 29, 1961, p. 257.
2. Clark, R. E., Orkin, L. R., Rovenstine, E. A. *J. Amer. med. Ass.* 1954, **154**, 311.
3. See *Lancet*, July 29, 1961, p. 272.

back to form the subject of further discussion. It may not be too much to hope that either the Ministry of Health or the Medical Research Council, or the Ministry through the Medical Research Council, will take the lead.

Department of Surgery, University of Liverpool. CHARLES WELLS.

SMOKING BY SCHOOLCHILDREN

SIR,—Your issue of Nov. 25 contains, under Public Health, yet another comment on smoking by schoolchildren. This repeated what has often been said before—namely, that there is an urgent need for increased anti-smoking education of schoolchildren and of the general population if the rising incidence of lung cancer is to be halted and reversed. Such anti-smoking education has been the function of local health authorities for the past three or four years, but there is little evidence that it is having any effect.

In my opinion the principal difficulty is that the power of the local health authority is limited, both in money and manpower, and that opposed to its efforts are those of the cigarette manufacturers who promote cigarette smoking with an energy that the local health authority cannot approach. Your issue of Oct. 28 contains the gist of an exchange in Parliament between Mr. Francis Noel-Baker and Mr. Niall Macpherson, parliamentary secretary to the Board of Trade. The latter was sceptical of the assertion that £20 million was spent on advertising tobacco in 1960 as compared with £1 million in 1953, but he did not deny that £7·7 million was expended on press and television publicity in 1960. The annual report (part I) of the Ministry of Health for 1960 (which, incidentally, devotes just 7 lines to smoking and lung cancer) also shows that local health authorities spent less on providing the midwifery service (£6·5 million) which delivered one-third of the nation's babies than the tobacco manufacturers spent on promoting the consumption of tobacco, and only a little more (£8 million) was spent on home nursing. The local authorities cannot in fact cope with this sort of expenditure devoted to one aspect only of health education, and we are fighting our battle with both hands tied behind our backs. Mr. Macpherson further denied that this advertising had been accompanied by any marked rise in tobacco consumption and gave the figure of 133 million lb. of tobacco smoked in the six months January to June, 1960, compared with 124 million lb. in the corresponding period of 1959. This is, in fact, a rise of 7%, so that the local authorities are making no headway at all!

The complacency of the authorities is difficult to understand. The number of deaths from lung cancer continue to rise from year to year. One can only conclude that even now the connection between smoking and lung cancer is not accepted in high places although, as Sir Derrick Dunlop is reported in *The Guardian* to have said last week (Dec. 1), "To deny that cigarette smoking is an important factor in the ætiology of lung cancer . . . is to carry scepticism to absurd lengths". The authorities are possibly afraid of losing the revenue from cigarette smoking, but surely it must be appreciated that even with the most energetic efforts the decline in cigarette smoking will be very gradual over the years.

Some help must be given to local health authorities. If, in the interests of liberty (so-called), the advertising industry is to be sacrosanct, then surely an energetic national campaign should be undertaken in the newspapers and on television on the same scale as is put forth by the tobacco manufacturers. Only in this way can we feel locally that our efforts are really worth while.

Public Health Department, Hadleigh, Essex. ALFRED YARROW Medical Officer of Health.

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide ('Distaval') with harmful effects on the fœtus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

THE CASUALTY DEPARTMENT

SIR,—Mr. Lamont (Nov. 25) lists a series of likely pitfalls which may befall a doctor but he talks as if these will inevitably beset him. Surely if a registered practitioner (as all casualty officers are) with a whole year of hospital training behind him has no idea how to deal with barbiturate poisoning or of the elementary rules of plastering the fault lies with the present method of medical education, not the method of staffing.

Mr. Lamont actually suggests in his proposed Utopia where all casualty officers will be consultants (able to cock a snook at all and sundry) that their work should be screened by the most junior casualty officer! He is in fact advocating that there should be a casualty department for the casualty department.

The idea that there should be a casualty consultant seems to me absurd. A specialist in not specialising I suppose. What would in fact happen if there were casualty consultants? Would they come to the department at 1 A.M. on a Saturday morning to decide whether or not the drunk has a head injury any more than the present consultants in charge of casualty departments do now? Of course not. Mr. Lamont knows this and so do I. If there is a serious doubt in the casualty officer's mind he will, as now, call in a registrar to help him—be he a medical, surgical, or orthopædic one.

Let me put the other side of the picture. I did casualty work and can honestly say that its very variety is a tonic. Of course one grumbles at the patient who comes to see you late at night complaining of an ache he has had for three days. It so happens that people are like that; and anyone who does not want to treat frail, erratic, stupid, inconsiderate, ungrateful, ill-mannered, but by and large pleasant, people, should take up pathology.

I think the present casualty arrangement is probably one of the most valuable training-grounds there is for any young man. Everyone has got to learn to take responsibility, and once he has registered the sooner the better. What better place than

in a hospital where usually the casualty sister knows what she is doing? (Well do I remember the day, looking anxiously at the unconscious victim of a road accident who appeared to be going rapidly into an even deeper coma, hearing the sister say "Anyone tried some glucose?") What else is general practice except casualty work under much more difficult conditions without any of the ancillary aids of the hospital or the reassurance of ever-ready help?

I agree that many attendances at casualty departments are unnecessary, but surely there is a ready solution to this problem. Engage the support of the general practitioners. How? By getting the general practitioners in each hospital district to do one day each as the casualty officer every few months. This would have several effects. It would lessen the number of unnecessary cases the general practitioner inflicted on his colleagues, until now a nameless casualty officer, but now a fellow general practitioner, who would be in a good position to retaliate or pinch his patients! Secondly, it would act as a continuous practical refresher course for general practitioners. Thirdly, it would bring the general practitioner back into the life of his local hospital; and fourthly, it would provide a steady supply of experienced casualty officers whom consultants would be only too glad to advise should the need arise.

West Middlesex Hospital, Isleworth. K. P. ABEL.

RESPIRATORY OBSTRUCTION DUE TO FAULTY CARLENS ENDOTRACHEAL TUBE

SIR,—Dr. Hayes (Nov. 25) points out a possible hazard of a Carlens catheter. Once, three years ago, I had the same trouble—right-sided obstruction when the tracheal cuff was inflated. I could not produce any useful inflation of the tracheal cuff without squashing the tube. This cuff had been repaired, so the manufacturers could not be held responsible for any structural defect.

Dr. Hayes uses the phrase "moderate distension of the proximal cuff (7–10 c.cm. of air)". The amount of air required is surely of little importance. The cuff should only be inflated until the anæsthetic gases just stop leaking back when the reservoir bag is compressed. Further inflation might damage the trachea or squash the tube. Only if the tube is squashed by inflation just sufficient to stop a leak would it be fair to blame the manufacturers. Is Dr. Hayes quite certain on this point? If so, then Blackpool has had a bad batch. I have always found that the manufacturing quality of the Carlens catheter has been of a consistently high standard.

London Hospital, E.1. J. V. I. YOUNG.

*** We showed Dr. Young's letter to Dr. Hayes, and his reply follows.—ED. L.

SIR,—The case which Dr. Young describes is simply an instance of overdistention of the tracheal cuff—a well-known hazard in endotracheal anæsthesia, which can be avoided if the standard practice in cuff inflation is followed.

Discussing inflation of the tracheal cuff, Dr. Young states that "the amount of air required is of little importance". On the contrary, this amount may be of critical importance, having regard to the relative sizes of the individual adult trachea and the standard Carlens catheter. If a relatively large volume of air is required to produce adequate cuff inflation in a wide trachea, then the intra-cuff pressure may be so increased as to balloon a thin internal or tube wall of the cuff into the right bronchial tube lumen. As I pointed out in my letter of Nov. 25, it is most usual for this obstruction to be a partial one resulting in a restriction rather than a dramatic blockage of the airway.

Inspection, palpation, and simple experimentation will reveal in many Carlens catheters the defect to which I have referred.

The high standards of manufacturing quality of the Carlens catheter are not in doubt, but the deficiency in the tube wall is a structural one inherent in a catheter of this design.

The hazard may be avoided by routinely checking the catheter airways before use, before and after inflating the cuffs right up to the estimated calibre of the individual tracheobronchial tree.

Victoria Hospital, Blackpool. BERNARD HAYES.

THE RADIO-IODINATED TRIOLEIN TEST

SIR,—Dr. Reith and his colleagues (Dec. 2) report that the test confirmed a diagnosis of steatorrhœa made on the basis of the clinical picture, laboratory tests, and response to therapy in 34 cases. This clinical evaluation was preferred to the use of more objective data, such as the orthodox fæcal chemical fat excretion, which the authors felt to be too inaccurate as a yardstick by which to judge radiotriolein absorption. In fact most authorities would agree that the fæcal chemical fat determination is at present the best means of assessing the presence and severity of fat malabsorption, particularly since stools with a high fat content may appear normal.

In spite of a constant flow of papers on the subject of radiotriolein, surprisingly few include a comparison of radiotriolein absorption with fæcal fat excretion. Several workers who have made this comparison have observed that the radiotriolein test may give a normal result when the fæcal fat excretion is abnormal.[1–4] In the face of such evidence few clinicians will be attracted to the radiotriolein test.

The reasons for the unreliability of the test are a matter of some interest and have been discussed extensively elsewhere.[1] One point made by Reith et al. is the importance of choosing the correct conditions for the administration of the dose of radiotriolein. The published evidence in this respect refers almost exclusively to normal subjects and suggests that the dosing procedure is unimportant. In my present studies in patients with steatorrhœa, there is little doubt that in these cases the fat load given with the dose of labelled fat makes a substantial difference to the absorption of the latter. Instability of the radiotriolein bond is another possible explanation of poor results with this material, and several authors seem to miss the point made by Van Handel and Zilversmit [5] that instability of this bond in the lumen of the gut may account for the different behaviour of orally administered ^{131}I and ^{14}C labelled fat. These and other problems are still in need of proper evaluation in man.

Radiotriolein has been used in the study of diseases unrelated to the alimentary tract including diabetes mellitus, atherosclerosis, cardiac failure, hyperlipæmia, and trauma. Reith et al. have added malignancy and depressions to this list, reporting low blood levels of radioactivity but normal fæcal excretion in both groups. One possible explanation of this finding is simple delay in gastric emptying, and this requires exclusion before a defect in fat absorption can be deduced.

Except in certain specialised fields, radiotriolein may well prove to be a disappointing tool for research-workers for two reasons. Firstly, it is an artificial material, and therefore good evidence that its behaviour reflects that of natural materials is required before it can be used as a substitute for the latter. Secondly, the rapid breakdown of the radioactive label after absorption is not in dispute, and therefore observations on radioactivity are a measure not only of fat metabolism but also of iodide metabolism.

The most valuable contribution in this field would be a convincing demonstration that radiotriolein can be used with

1. Cox, A. G. *Brit. med. J.* 1961, ii, 933.
2. Jones, R. V. *ibid.* 1960, ii, 1236.
3. Pimparker, B. D., Tulsky, E. G., Kalser, M. H., Bochus, H. L. *ibid.* p. 894.
4. Rufin, F., Blahd, W. H., Nordyke, R. A., Grossman, M. I. *Gastroenterology*, 1961, **41**, 220.
5. Van Handel, E., Zilversmit, D. B. *J. Lab. clin. Med.* 1958, **52**, 831.

confidence in the clinical investigation of steatorrhœa, and this must surely include well-documented evidence of the nature of the cases studied.

University Department of Surgery,
The Royal Infirmary,
Sheffield. A. G. Cox.

HÆMOPHILIA A IN A GIRL

SIR,—de la Chapelle et al.[1] reported an interesting case of severe hæmophilia A in a girl who was clinically and cytologically a normal female.

They suggest three possibilities: that the girl's real father was a hæmophiliac; that non-disjunctions occurred both in father and mother; and that hæmophilia mutation occurred in the X-chromosome of the father. If any one of these assumptions, although they seem very improbable, were accepted, it would explain the formation of a homozygous hæmophiliac female but not why she survived. It is generally accepted that homozygous hæmophiliacs invariably die at some stage of the fœtus, and this is why hæmophiliac females are so rare.

To meet this difficulty, I suggest that in one of the parents mutation to a new gene occurred, which enabled the hæmophiliac gene to manifest phenotypically the characteristic symptoms even in the heterozygous condition in a female. It does not matter where the mutation took place, in father or mother, in X chromosome or autosomes.

National Institute of Genetics,
Misima, Sizuoka-ken, Japan. YOSHIMARO TANAKA.

HALOTHANE

SIR,—The condition referred to by Dr. Massey Dawkins (Dec. 2) as " the halothane shakes " is common, but is it a true side-effect of the drug? I can remember a similar condition in the days when ether was virtually the sole agent before the advent of intravenous barbiturates, but it was neither so frequent nor so severe. In more recent times a very similar condition was seen after hypothermia. This was very severe and prolonged, and in order to avoid its occurrence in these cases the practice of rewarming under anæsthesia was successfully adopted.

It seems reasonable to regard these conditions of shivering as reactions to heat loss. Halothane, being a potent anæsthetic, is often given after induction by a minimal dose of barbiturate, and sometimes, as in the case cited by Dr. Dawkins, with no barbiturate induction. Bearing in mind the rapid elimination of halothane, it does not seem surprising that there should be a reaction to heat loss in these cases before the effect of a warm bed has had time to render such a reaction unnecessary.

The absence of shivering after the barbiturate/nitrous-oxide/oxygen sequence is probably due to the fact that more barbiturate is used and often pethidine as well, in order to give adequate sedation and analgesia, and that these drugs, taking longer to be eliminated, inhibit the onset of shivering until the heat lost has been regained.

How could the condition be avoided? I believe that rewarming before discontinuing anæsthesia would be a complete answer but would be hardly practicable in all cases in view of the time, space, and staff which would be required; but it might well be practised in selected serious cases. Something might be done to reduce heat loss by warmer theatres and more efficient covering of patients.

In general, however, I think that much of this difficulty could be avoided were we to be slightly more liberal with intravenous sedation. It is in some ways satisfactory to see a patient recover consciousness before leaving the theatre, but in most cases it means that postoperative sedation for pain must be given all the sooner; and if this rapid recovery is to be paid for by a period of shivering, which must be to some extent exhausting, surely the price is too high.

Royal Free Hospital,
London, W.C.1. JOHN H. WILLIS.

1. de la Chapelle, A., Ikkala, E., Nevanlinna, H. R. *Lancet*, Sept. 9, 1961, p. 578.

DISCS, LESIONS, AND SYNDROMES

SIR,—Dr. Dalgleish (Nov. 11) quotes work done here on the chemical changes associated with disc prolapse [1] and asks whether these and the prolapse might not be secondary to an abnormality elsewhere in the intervertebral-joint complex. Mr. Webster-Jones (Nov. 25) puts forward a similar, but more emphatic, claim that disc " degeneration " is the result, and not the cause, of joint fixation. While Dr. Mitchell and I would have accepted this tentatively as one of several possible explanations of our findings, we now have strong evidence in another direction: as it will inevitably be some months before this appears in print, I write now in case our previous work should be taken as supporting a hypothesis which we have never advanced, and would now reject.

Briefly, we find that patients with disc prolapse show a low polysaccharide content not only in their affected nucleus pulposus but also in their lumbodorsal fascia, and that their blood levels of protein-bound hexose, hexosamine, and glucuronic acid are significantly elevated, particularly during the acute phase. We conclude that disc prolapse is a local manifestation of a generalised disturbance of metabolism, the cause of which is unknown, but which is probably in the nature of a disordered acceleration of polysaccharide catabolism, and which may be responsible also for other disorders often clinically associated with those of the disc, such as rotator-cuff lesions. These conclusions must remain provisional until further work is done, but it does at least seem certain that a mechanistic concept of disc prolapse can no longer be sustained.

One somewhat depressing corollary of this and of our previous work is that the restoration of normal physiological function to a prolapsing disc is at present impossible, and will so remain until a means is found of reversing the biochemical abnormality just described. The process of clinical cure being no more than the process of replacement fibrosis, I can see no scientific basis for any treatment in the acute phase other than the orthodox immobilisation by plaster, or a brace, or in traction, with operation for those few patients in whom severe nerve pressure persists or recurs.

This having been said, I must add my strong agreement to the views about the necessity of viewing the intervertebral disc as merely one part of the intervertebral-joint complex: restriction of movement within it cannot be, to my mind, a source of disc prolapse but it is equally certainly the source of a great deal of subsequent disability. For some years now, my teaching has been that fibrosis of the prolapsed disc having meanwhile to be accepted, and having once been achieved by immobilisation, nothing is thereafter more essential than to mobilise the affected spinal segment. Acceptance of a significant restriction of movement there (which may perhaps mistakenly be advocated as an insurance against further prolapse) can only lead, on the basis of the most orthodox pathology, to osteoarthritis of the apophyseal joints, and so to further fibrosis: I suspect that there must have been many recurrent episodes of root pressure attributed to " the disc above ", which occurred in fact in the intervertebral foramen at the old level of prolapse. Whether or not this is the " osteopathic lesion " to which Dr. Dalgleish and your other correspondents refer, I do not know: I can only say that in my own experience it responds to a regimen of graduated active exercise, reinforced, where the restriction proves obdurate, by a purely rotatory manipulation under an anæsthetic. The same regimen ought, on first principles, to be the routine after-treatment when a brace or plaster jacket is discarded.

May I add a plea (not for the first time) for the abandonment of the word " degenerative " to describe the nuclear changes that precede prolapse? There is now no possible reason to confuse these with the effects of age; nor indeed to suggest that normal ageing, which has every appearance of being a

1. Mitchell, P. E. G., Hendry, N. G. C., Billwicz, W. Z. *J. Bone Jt Surg.* 1961, **43B**, 141.

beautifully balanced mechanism, should be thought comparable to the degeneration (properly designated) which is the late after-effect of almost any pathological process. The term "prolapsing disc", as used above, seems to me to be an adequate description of that prodromal state in which a hydrostatically unstable nucleus is contained within an abnormally distensible annulus, but may perhaps be thought to beg the question. "Depolymerised" would describe the truth, but not the whole truth: "dys-absorptive" would describe the disturbance in physics: "nucleopathic" is perhaps at once too narrow and too unspecific. If a small note of national prejudice may be allowed to obtrude on an otherwise wholly objective letter, I might remark that, if the northern branch of Insular West Teutonic had become as widely used as the southern (as its flexibility and expressiveness deserve) then "disjaskit" would have met the need completely.

Royal Infirmary, Aberdeen. NEIL G. C. HENDRY.

CHILD PSYCHIATRY

SIR,—I must draw attention to an apparent misrepresentation of the views of undergraduate teachers of psychiatry which appeared in the memorandum in your issue of Dec. 2 (p. 1249). As originally presented to the general meeting of the Association of Undergraduate Teachers of Psychiatry the memorandum you printed contained a statement to the effect that the best site for a child-guidance clinic is a pædiatric hospital. This view was challenged by many of the members present—among other reasons because a very critical period for children is puberty, because the child psychiatric service needs to be integrated with the developing service for adolescents, and because the psychiatric treatment of children sometimes requires adequate facilities for the psychiatric treatment of adults. It was agreed that this recommendation should be changed to the sense that child psychiatric clinics could best be sited "either in a pædiatric hospital or in a general hospital *with* a pædiatric department", not "in a general hospital *within* a pædiatric department".

The Royal Free Hospital, North Western Branch, London, N.W.3. ALICK ELITHORN.

ASTHMA

SIR,—We were largely in agreement with the views in your editorial of Aug. 19, except for the final statement that "the treatment of bronchial asthma remains mainly symptomatic". We have found that, if the infection in the respiratory apparatus be controlled, the asthmatic attacks cease, usually without further attempts to eliminate specific external allergens, or to densensitise the patient to these offending materials.

Thus, we find that the crux of the matter is reached in your statement that "the disposition of antibodies depends (also) on . . . the presence of inflamed tissue (in which they tend to accumulate) . . ." and ". . . the possibility that antibody is localised in inflammatory tissue". We aim our antibacterial attack against staphylococcal infections, since these seem to be the most frequent, persistent, and virulent of the offenders. Thus, McDermott [1] states, "As we all know, the three principal diseases involving bacteria that are now prominent in the United States are those diseases produced by the bowel flora, the tubercle bacilli, and by staphylococcus." The same writer goes on to say that "approximately one-half of any group of adults . . . are nasal carriers of staphylococci . . . The percentage harbouring staph. at any one time or another rises and may reach 70–80%". In view of the apparently almost inevitable appearance of strains resistant to each and every new antibiotic, and because we have found an effective method of treating chronic or recurrent staphylococcal infections, during the past eight years, we have used staphylococcal bacteriophage lysate (S.P.L.).

The live bacteriophage in this product may or may not bring about immediate destruction of some of the organisms present, but probably the principal effect is due to the stimulation of antibody formation and resistance to infection, the response to the antigenic substances in the lysate produced by the destruction of the staphylococci in which the phages are cultured.

New Vernon, New Jersey. MARGARET SYMONDS.
Short Hills, New Jersey, U.S.A. GEORGE G. SALMON, JR.

1. McDermott, W. *Ann. N.Y. Acad. Sci.* 1956, **65**, 57.

AN EARLY IRON LUNG

SIR,—In the opening paragraph of his article of Nov. 18, Dr. Kelleher refers to Drinker introducing the "iron lung" in 1929. Your readers might be interested in the illustrations in your journal [1] of a much earlier iron lung devised by Woillez. The principle of his "spirophore",[2] which preceded Drinker's apparatus by 53 years, is clearly the same. Nevertheless, although Woillez visualised the use of his cabinet respirator for prolonged as well as brief apnœa, I have not come across any reference to its being used for the prolonged treatment of respiratory failure.

Nuffield Department of Anæsthetics, The Radcliffe Infirmary, Oxford. H. G. EPSTEIN.

TREATMENT OF MULTIPLE SCLEROSIS WITH CORTICOTROPHIN

SIR,—Dr. Kelly and Dr. Jellinek (Dec. 2) raise an interesting point on "pairing", in their comments on our trial of corticotrophin (A.C.T.H.) in the treatment of exacerbations of multiple sclerosis.

We considered employing this method when we designed our observations, but our final decision to compare groups of patients randomly allocated to corticotrophin and control groups, rather than to attempt to select similar "pairs" of exacerbations and make a within-pair comparison, was quite deliberate. The course of this disease is so variable that even to "pair" patients on the basis of their history and physical status at the start of an investigation is difficult enough, but we believe that to "pair" acute episodes would be frankly impossible. In exacerbations of certain other diseases the best control is the patient's previous or successive attack, but in multiple sclerosis succeeding exacerbations may vary so widely in form and severity that even this method is denied us. We believe that if cases are fairly allocated by an acceptable random method, overall comparison of responses in the two groups is the correct method of analysis. Although subdividing groups can give valuable results in large-scale trials it is rarely profitable to attempt subanalyses in a small trial such as this, since the subtrial groups are even smaller.

Nevertheless, to allay the doubts raised by Dr. Kelly and Dr. Jellinek we can offer the following subanalyses:

(1) In our trial, there was no evidence of association between age and response to treatment, making subdivision by age unnecessary. Nevertheless, if two age-groups divided at the median age of 35 are used, numbers in the two groups are small and the effects of corticotrophin cannot be demonstrated significantly in either group.

Age-standardisation on the basis of these two age-groups shows the chance of a good (A) response to be significantly higher for corticotrophin than for the controls ($P < 0{\cdot}05$).

(2) Since there were only 8 first episodes (divided 6:2 between corticotrophin and controls) the possibility of bias can best be tested by eliminating these 8. The association between corticotrophin and a favourable response is demonstrated in the remainder, with a slightly increased χ^2 value.

1. *Lancet*, 1939, i, 237.
2. *Bull. Acad. Méd., Paris*, 1876, **5**, 611.

(3) In the 18 " deteriorations of existing disability ", despite small numbers, the favourable corticotrophin response is significantly demonstrated. It is not demonstrated significantly amongst the remainder.

HENRY MILLER
D. J. NEWELL
ALAN RIDLEY.

Royal Victoria Infirmary,
Newcastle upon Tyne.

OBSERVATIONS ON THE SATELLITED HUMAN CHROMOSOMES

SIR,—In their comments on our article [1] with this title Dr. Petersen and Dr. Therkelsen [2] question the validity of our definition of a satellited chromosome, and imply that " distinct chromatin knobs " and " negative heteropyknosis at the ends of the chromosome arms " need not, as we affirm, be manifestations of the same phenomenon. Our observations indicate that satellited regions vary in their morphological appearance and degree of heteropyknosis under conditions at present only partially apparent, and lead to the conclusion that all chromosomes in groups IV (13–15) and VII (21 and 22) are potentially satellited. Additional evidence for this may be found in the answers to the three questions posed by Dr. Petersen and Dr. Therkelsen.

The first question inquires about the proportion of satellited chromosomes which appear as " distinct chromatin knobs " rather than areas of negative heteropyknosis. As shown in table I, the proportion of " distinct knobs " found in the three

TABLE I—TYPE OF SATELLITE REGION PRESENT IN UNSELECTED GROUP IV AND GROUP VII CHROMOSOMES IN 150 CELLS FROM THREE INDIVIDUALS

—	Definition of satellite		No visible satellite	Total
	Negative heteropyknotic region	Distinct chromatin knobs		
Group-IV chromosomes	572 (63·6%)	112 (12·4%)	216 (24·0%)	900
Group-VII chromosomes	359 (56·8%)	56 (9·3%)	185 (30·8%)	600

pairs of group-IV chromosomes is not very different from the proportion found in the two pairs of group-VII chromosomes, in each group the satellite appearing as a " negative heteropyknotic region " approximately 5–6 times more frequently than as " distinct knobs ". These figures are consistent with *all* chromosomes in both groups being potentially satellited.

In answer to the second question, we have never seen 10 chromosomes with distinct chromatin knobs in any one diploid cell. Needless to say, had we done so, none of the tedious counts recorded in tables I and II of our article would have been necessary. One photograph would have been sufficient.

The answer to question 3 is yes. We have on four occasions noted cells in which five group-IV chromosomes have satellites which appear as " a secondary constriction with distinct chromatin knobs projected from the arms on slender stalks ".

Table II is presented as evidence that one satellited region may vary in morphological appearance and show different degrees of heteropyknosis from one cell to another in a particular individual. One of us (S. D. H.) has examined material from three individuals in which a satellited chromosome in group IV, or group VII, or both groups, can be readily distinguished from other chromosomes in the same group because of the differential size of the satellite. In each case this satellite region can be identified either as larger isopyknotic knobs, or as larger negatively heteropyknotic knobs, or as larger areas of negative heteropyknosis.

Observations on satellite association also tend to confirm that all groups IV and VII chromosomes are potentially satellited, for we have several times observed a cell in which all group-VII chromosomes or all group-IV chromosomes are involved in

1. *Lancet*, 1961, i, 638.
2. *ibid.* p. 1229.

TABLE II—DEFINITION AND DEGREE OF HETEROPYKNOSIS OF THE SATELLITE REGION IN A SPECIFIC CHROMOSOME, IDENTIFIABLE ON ACCOUNT OF A LARGE SATELLITE (50 cells in each case)

—	Negative heteropyknotic region	Distinct knobs	
		Negatively heteropyknotic	Isopyknotic
Group-IV chromosome (case 1)	29	20	1
Group-VII ,, (case 1)	44	6	0
Group-IV ,, (case 2)	29	17	4
Group-VII ,, (case 2)	33	12	5
Group-VII ,, (case 3)	29	12	9

satellite association. In passing we might add that we have heard confirmation of the phenomenon of satellite association from many investigators. It appears also that this phenomenon is not confined to man, as one of us has made similar observations in the chimpanzee (M. A. F.-S., unpublished), and we hear that it has been seen in swine cells (Dr. Frank H. Ruddle, personal communication).

We have noted elsewhere that secondary constrictions in non-satellited chromosomes either appear as regions of negative heteropyknosis or as isopyknotic constrictions, or merely as regions associated with satellited chromosomes.[3] In their variable degree of heteropyknosis they are very similar to the satellite regions in the chromosomes of groups IV and VII.

Division of Medical Genetics,
Department of Medicine,
Johns Hopkins University
School of Medicine,
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MALCOLM A. FERGUSON-SMITH
STANLEY D. HANDMAKER.

CONTAINER FOR CULTIVATING BLOOD FOR CHROMOSOME STUDIES

SIR,—An important step in the cultivation of white blood-cells by the technique of Moorhead et al.[4] is the separation of the red cells from the plasma containing the white cells. When the amount of supernatant plasma is small it is important to make the most of it and avoid contamination with red cell.

The container.

I have found it useful in these cases to use a glass container with a constriction in the middle (see figure). The heparinised blood is put directly in this container, and after centrifugation the interface between plasma and red cells is at the narrow part of the container; this makes it easier to obtain the maximum amount of red-cell-free plasma.

Central Hospital, Eskilstuna,
Sweden.

KURT KAIJSER.

ACRIDINE ORANGE AS A CHROMOSOME STAIN

SIR,—One of the problems associated with the interpretation of small chromosomal fragments in the human cell cultures is the presence of non-chromosomal debris in the microscopic fields. Two of us (L. M. S. and T. V.) have developed a method for staining human chromosomes with acridine orange, which offers the advantages of good contrast and the absence of stained artefacts. Although the method will be published in detail elsewhere, your readers may care to have a brief account of it.

Chromosome preparations were made from leucocytes cultured by the method of Moorhead et al.[4] They were allowed to air-dry on non-fluorescent slides. The chromosomes were fixed to the slides with absolute methyl alcohol, and the slides were progressively transferred through diminishing concentrations of ethyl alcohol and finally to distilled water. They were then placed in McIlvaine's buffer, pH 6·4, stained with 0·01%

3. Ferguson-Smith, M. A., Handmaker, S. D. To be published.
4. Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., Hungerford, D. A. *Exp. Cell Res.* 1960, **20**, 613.

acridine orange in buffer for two minutes, and put through two more changes of buffer. A non-fluorescent cover slip was used. A Leitz Labolux microscope was used with an Osram HBO 200 mercury-vapour lamp as the illuminator. For black-and-white photographs, using Kodak Plux-X film (ASA-160), an exposure of 20–25 seconds gave good results.

Chromosomes and nuclei stained by this method fluoresce light green to yellow against a black background, while the cytoplasm of non-dividing cells and ribonucleic acid fluoresces red. The preparations may be sealed with wax and used for long periods of time without significant deterioration. After observation with fluorescent microscopy the slides may be destained with methyl alcohol and restained with acetic orcein if permanent preparations are desired.

This work was aided by a fellowship from the National Cancer Institute and by grants from the National Institute of Arthritis and Metabolic Disease.

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LEWIS M. SCHIFFER
TIIU VAHARU
LYTT I. GARDNER.

VISITING MOTHER IN HOSPITAL

SIR,—Visiting of children in hospital is now, at least in theory, encouraged. Visits by children to their mothers in hospital are usually forbidden. I cannot see any reason for this except prejudice and would be interested to learn the views of others.

It seems particularly unfortunate that young children should be prevented from visiting their mothers when they are in hospital for the birth of the next child.

Farnborough, Kent.

D. G. LEYS.

ACCIDENTAL HYPOTHERMIA

SIR,—In their article (Dec. 2) Dr. Helen Duguid and her colleagues include five examples of myxœdema in their total of twenty-three cases, and comment on the difficulty of distinguishing patients with myxœdema and normal blood-cholesterol from euthyroid patients, at least one of whom looked " myxœdematous " during the period of hypothermia but later reverted to a normal appearance without thyroid therapy.

One wonders how the diagnosis of myxœdema was excluded in the eighteen patients to whom other associated and precipitating factors were attributed. This was clearly not done on clinical grounds, nor on blood-cholesterol levels; nor is the thyroid referred to in the account of histological findings. If the criteria were the absence of a previous diagnosis of myxœdema, or reversion to normal without thyroid therapy, then these are insufficient grounds for rejecting hypothyroidism.

The concept of " acute myxœdema ", recently propounded by Hausmann and Karlish,[1] may be in part fallacious, since it is often the recognition rather than the onset which is " acute ". Yet it is quite conceivable that a patient whose thyroid function is poor, but just sufficient for everyday needs, might be precipitated into overt hypothyroidism by exposure to cold or respiratory infection, and equally might revert to a euthyroid state when the precipitating factor has ceased to operate. It is notable that Minjer,[2] in his study of hypothermia occurring in Holland towards the end of the late war, found histological changes indicating inadequate thyroid function in all four of his adult cases, although only one had been clinically myxœdematous.

The age range and sex distribution of the patients described by Dr. Duguid and her colleagues are in keeping with those of myxœdema, and it is likely that at least some of them suffered from occult hypothyroidism. It would have been interesting to know something of the state of the thyroid in the thirteen cases which came to necropsy.

Since no other explanation is proffered for the " myxœdematous " features of the elderly woman depicted in fig. 4, the most probable reason is that she was indeed myxœdematous.

Department of Pathology, University of Manchester.

G. SCLARE.

1. Hausmann, W., Karlish, A. J. *Brit. med. J.* Oct. 21, 1961, 1063.
2. Minjer, A. de *J. Path. Bact.* 1952, **64**, 741.

RESPONSE OF NORMAL SUBJECTS TO TEST DOSES OF FRUCTOSE

SIR,—Dodds and his coworkers [1 2] have measured the circulating levels of total reducing substances, glucose, pyruvate, and lactate in healthy young adults given test doses of dextrose, sucrose, and liquid glucose. Of these sugars, sucrose gave the highest levels of pyruvate and lactate, owing presumably to the hepatic metabolism of fructose. In limited observations with fructose itself, they have found appreciably higher 90-minute pyruvate levels than those from dextrose.

We have extended these observations by comparing the effects of dextrose, sucrose, and fructose in 15 normal young adults. In 6 of these we have determined the circulating levels of glucose, pyruvate, lactate, and fructose (by the method of Scott,[3] modified so as to use 2 ml. of whole blood).

The results after doses of 50 g. dextrose or sucrose are in close agreement with those of Dodds. In the case of fructose, there appears to be almost immediate partial conversion to glucose, which is circulating as such in samples taken 15 minutes after dosing. The bulk of the fructose, however, appears to be represented by non-glucose reducing substances, including pyruvate and lactate, which attain their maxima 60–90 minutes after dosing. The mean peak increases (mg. per 100 ml.) above fasting level in our series were, for lactate, 4·57 after dextrose, 6·33 after sucrose, and 9·0 after fructose, and, for pyruvate, 0·53 after dextrose, 0·92 after sucrose, and 1·07 after fructose.

Very little fructose appears to circulate as such, but simultaneous capillary and venous samples indicate that it passes into the tissues. Only about 0·3% of the ingested dose appears in the urine in the subsequent 120 minutes.

These results will be published in detail elsewhere, with discussion of their significance. We are grateful to Dr. A. C. Miller and Mr. C. F. M. Rose, of the Courtauld Institute of Biochemistry, for their helpful advice on fructose estimations.

J. S. LEAHY
P. R. B. NOEL
A. E. STREET
A. N. WORDEN.

Nutritional Research Unit, Huntingdon.

CONGENITAL MALFORMATIONS OF THE EXTREMITIES

SIR,—In 13 sibships we have studied 15 cases (9 males and 6 females) of multiple bone aplasias and hypoplasias and congenital " amputations " of the extremities.

They included abnormalities of different extent, such as manus vara, total amelia, upper extremity amelia, phocomelia, and above-elbow congenital " amputation " associated with foot defects. All the parents were normal. Only one propositus had sibs with a similar defect. In no instance did other members of the family show an abnormality identical to that found in the propositus. In 3 families, different congenital anomalies were also found among the propositus's relatives. None of the 13 sibships was the offspring of a consanguineous marriage.

Although cases of bone aplasia and hypoplasia and congenital " amputation " of the extremities have been found to

1. Dodds, E. C., Fairweather, F. A., Miller, A. L., Rose, C. F. M. *Lancet*, 1959, i, 485.
2. Dodds, E. C., Miller, A. L., Rose, C. F. M. *ibid.* 1960, ii, 178.
3. Scott, L. D. *Biochem. J.* 1935, **29**, 1012.

be due to autosomal recessive genes,[1 2] it is clear that no simple genetic mechanism is responsible for those here reported.

We are grateful to our colleague, A. Quelce-Salgado, for data on one of the families.

Laboratório de Genética Humana,
Universidade do Paraná,
Curitiba, Pr, Brazil.

N. FREIRE-MAIA
A. FREIRE-MAIA.

PREVENTION OF PRESSURE SORES

SIR,—I agree with Dr. Bedford (Dec. 2) that it is important to distinguish two types of bedsore. Groth [3] has described the features of the deep or malignant sore which starts with necrosis of the underlying tissues and only later breaks through the skin, and of the much less serious superficial sore where the tissue damage is confined to the skin. Nevertheless, pressure plays a significant part in the causation of superficial sores, although other factors, such as contact of urine with the skin of incontinent patients, may also be concerned. In our series the two types of sore have been included.

Our studies indicate that approximately 20% of the patients newly admitted to a geriatric unit are especially at risk, and by distinguishing these patients it is possible for the nurses to concentrate their attention on this group. Indeed the deployment of nursing skills for patients who most need them and the prevention of such complications as pressure sores present strong arguments in favour of the adoption of schemes of progressive patient care in geriatrics. Using such a scheme, a description of which is to be published,[4] a reduction in the overall incidence of pressure sores to 6·5% has been achieved.

Whittington Hospital,
London, N.19.

A. N. EXTON-SMITH.

TEENAGE MORALS

SIR,—Dr. Comfort's advocacy [5] of earlier sexual freedom on the grounds of a steady fall in the age of physical puberty and as a solution to the problem of delinquency and teenage morals of our day ignores the inherent biological differences in male and female sexuality. In simple language, Dr. Comfort is proposing that sexual behaviour in women should be a matter of volition rather than of morality, to be indulged in as the urge arises, for this would be the only "sensible" and "normal" conduct in our sophisticated civilisation.

Dr. Comfort assumes that male sexual behaviour and female sexual behaviour are identical. They are not identical; they are complementary. One is male, and the other is female. The ethical and moral structure of the human race and civilisation throughout ages has evolved around the basic differences in male and female sexuality. The male behaviour is an intense, explosive, periodically recurring urge which is satiated by the discharge of spermatic fluid. The male is by nature a Don Juan and does and will settle down for economic, social, moral reasons and also for convenience. The female behaviour does not terminate in becoming a joyous receptacle for spermatozoa, even if they were received under the most romantic circumstances, to be sustained or destroyed as the circumstances might dictate. A woman's true sexuality begins when that of her partner has already ended. It is completed and fully gratified when the initial act is followed by pregnancy, childbirth, and nursing under the loving care of the man whom she regards as the proud and the lawful father of her brood. All those who would argue in favour of limiting sexual activity to a phase wherein intercourse would be the final act for both partners, *ipso facto* consider it to be of little importance to provide children with a legitimate father as well as a mother. Widespread use of contraceptives by the unmarried can and will eliminate pregnancy and its sequelæ, which are conditions already being looked upon by many with embarrassment in the least. Such "liberation" or "masculinisation" of the role of the female would be highly conducive to the emergence of a generation of females for whom the very thought of pregnancy or even marriage would be repugnant. We have already succeeded in breeding a generation of females incapable of secreting enough milk to nurture their own babies and whose mammæ have largely become ornamental appendages for erotic delight.

Such "lores" of liberation have been put to practice by past generations of men with catastrophic consequences for the survival of their race and mores. Sexual freedom of the type advocated by Dr. Comfort caters to the sexual "lore" of the atomic era, one which is condoned and is already practised in Scandinavian countries. I have not yet come across statistical reports which would compare the academic achievements of emancipated youth and their stability and contentment, as well as the wholesomeness of family life, in these countries with a country like Switzerland with its so-called "old-fashioned" mores and taboos.

Loudonville, N.Y.

D. A. BERBERIAN.

ESSENTIAL FATTY ACIDS AND CORONARY HEART-DISEASE

SIR,—Like most other writers, Professor Yudkin[1] accepts as almost certain that in Britain there has been no increase in incidence and severity of coronary atherosclerosis over the past 50 years. This conclusion stems from one investigation—namely, that undertaken at London Hospital over the period in question.

The study involved the careful examination of postmortem records providing description and assessment of lesions, particularly of calcification, in the coronary vessels.[2] Actually, the evidence in question revealed "a substantial decrease of advanced coronary atheroma". I think that it must be recognised that the situation in this area of research (changes in arterial atherosclerosis) is confused to say the least.

In disagreement with the British study is the conclusion of an investigation in New York,[3] which indicated that coronary atherosclerosis has greatly increased within the past 25 years, the increase appearing to parallel the rise in mortality from coronary heart-disease (C.H.D.). Evidence from war-time Scandinavia [4] and Holland,[5] and from post-war Berlin,[6] indicate that there was a reduction in intensity of coronary atherosclerosis, associated with the period of food privation. In Austria,[7] however, it was concluded that "5 years of war was equivalent to 20 years of peace-time in causing sclerosis (coronary sclerosis) in younger men, but undernutrition prevented advanced sclerosis and infarction in older men." From Dachau concentration camp,[8] necropsies indicated extensive arteriosclerosis (not defined): "The degree of arteriosclerosis was related to the length of time in the concentration camp . . . changes were chiefly in the endocardium and coronary arteries, along the whole length of the aorta, and in the cerebral vessels." The work of Wilens [9] indicated a lower incidence of atherosclerosis in patients dying from wasting diseases.

How can these items of evidence be reconciled? Obviously,

1. Freire-Maia, A., Freire-Maia, N., Quelce-Salgado, A. *Proc. X Int. Congr. Genet., Montreal*, 1958, vol. II, p. 88.
2. Freire-Maia, N., Quelce-Salgado, A., Koehler, R. A. *Acta genet.* 1959, **9**, 33.
3. Groth, K. E. *Acta chir scand.* 1942, suppl. 76, p. 87.
4. Exton-Smith, A. N. *Lancet* (in the press).
5. *ibid.* 1961, i, 1335.

1. Yudkin, J. *Practitioner*, 1961, **187**, 150.
2. Morris, J. N. *Lancet*, 1951, i, 1, 69.
3. Spain, D. M., Bradess, V. A. *Amer. J. med. Sci.* 1960, **226**, 710.
4. Biorck, G. *in* Cardiovascular Epidemiology; p. 8. New York, 1956.
5. Schornagel, H. E. *Docum. Med. geograph. trop.* 1953, **5**, 173; *Nutr. Abstr. Rev.* 1954, **24**, 193.
6. Pezold, F. A. *in* Atherosclerosis and Nutrition; p. 246. Darmstadt, 1959. Reviewed in *Amer. J. clin. Nutr.* 1960, **8**, 384.
7. Barnes, B. O., Ratzenhofer, M. *Fed. Proc.* 1961, **20**, 97.
8. Blaha, F. *Cas. Lék. Ces.* 1958, **97**, 85; *Nutr. Abstr. Rev.* 1958, **28**, 888.
9. Wilens, S. L. *Arch intern. Med.* 1947, **79**, 129.

with advances in the classification of lesions, some clarification may be expected. Our investigations [10] suggest that percentage of mineral matter (especially calcium) in arterial tissue may provide a more objective index of atheroma than naked-eye appraisal of lesions. But knowledge is incomplete: for example, we urgently need to know whether there is or is not a gross difference in the coronary atherosclerosis picture at London Hospital,[2] compared with Presbyterian Hospital, New York City,[3] as the cited publications suggest.

Yudkin refers again [1] to the increase in mortality from C.H.D. in Britain paralleling that of increase of licenses issued for radio and television. His earlier view [11] has been commented on by a number of writers, recently by Keys,[12] to whom he may be replying.

He mentions the limited correlation between total fat intake and mortality-rate from C.H.D., and states that correlation is no better if attempts are made to differentiate between saturated and unsaturated fats. This conclusion is at variance with that of Bronte-Stewart,[13] who holds that " qualitative rather than quantitative differences in the dietary fat intake could explain better the reported differences in mortality from the disease."

The statement that the Japanese are said to have as much atherosclerosis as white Americans is hardly true. In one investigation, postmortem studies have indicated that severe coronary atherosclerosis in Japanese men is about a tenth of that of white Americans.[14] Furthermore, Yudkin's statement that there is still some doubt whether the South African Bantu have much or little atherosclerosis is also incorrect. Every large postmortem series has amply demonstrated that atherosclerosis certainly occurs among the Bantu, but that the incidence and severity, and certainly the complications in so far as C.H.D. is concerned, are less than they are in white populations.[15]

Yudkin refers to the anomalous situation regarding fat intake and C.H.D. among Indians in Kenya. Now, according to Charters and Arya,[16] the Gugerati Indians (vegetarian) in Nairobi consume about 100 g. fat per day, whereas the Punjabi Indians (non-vegetarian) consume about 130 g. fat per day. I certainly do not regard 100 g. as a " little " fat intake. Furthermore, C.H.D. mortality among both groups is not " low ", it is high [17]; indeed, among immigrant Indian groups elsewhere, whether in Singapore, Kampala, Johannesburg or Durban, C.H.D. mortality-rates among males are among the highest in the world.[18]

With the main burden of Professor Yudkin's paper [1]—namely, that the part played by deficiency of essential fatty acids in the pathogenesis of C.H.D. is far from established—there can be no quarrel. I think, with Professor Yudkin, that the study of populations providing exceptions, real or apparent, to current hypotheses can be very salutary. In Johannesburg, with 600,000 Bantu, we have a moiety of prosperous persons, owning motor cars; we have many old Bantu; we have some Bantu with high serum-cholesterol levels (over 300 mg. per 100 ml.), with long blood-clot-lysis times, with severe arterial lesions, and with hypertension.[19] Yet at Baragwanath Hospital (2000 beds), there is so far an average of about 1 death per year from myocardial infarction.[20] Further north, in certain regions, among indigenous African groups, there are very high consumers of animal fat[21]; yet our inquiries, direct and indirect, do not suggest a high incidence of C.H.D. among them; and this impression is supported by Salomon.[22] It remains our hope that the study of populations of the type described, and of populations in transition, may contribute valuable information.

The studies mentioned are being financed in part by a grant from the National Heart Institute, United States Public Health Service.

South African Institute for Medical Research, Johannesburg, South Africa. ALEXANDER R. P. WALKER.

10. Andersson, M., Walker, A. R. P., Lutz, W., Higginson, J. *Arch. Path.* 1959, **68**, 380.
11. Yudkin, J. *Lancet*, 1957, ii, 155.
12. Keys, A. *Circulation*, 1961, **23**, 805.
13. Bronte-Stewart, B. *Brit. med. Bull.* 1958, **14**, 243.
14. Keys, A., Kimura, N., Kusukawa, A., Bronte-Stewart, B., Larsen, N., Keys, M. H. *Ann. intern. Med.* 1958, **48**, 83.
15. Becker, B. J. P. *Lancet*, 1958, ii, 1019.
16. Charters, A. D., Arya, B. P. *ibid.* 1960, i, 288.
17. Charters, A. D. *ibid.* 1961, i, 773.
18. Walker, A. R. P. *ibid.* p. 512.
19. Walker, A. R. P. *Amer. J. clin. Nutr.* 1961, **9**, 461.
20. Isaacson, C., Seftel, H. C., Schamroth, L., Keeley, K. J. *Lancet*, July 1 1961, p. 50.
21. Walker, A. R. P. *Brit. med. J.* 1960, i, 1660.

COLLES' FRACTURE

SIR,—I must share with Mr. Stone (Dec. 9) his astonishment at your annotation of Oct. 28. Anyone who has had years of experience in the treatment of Colles' fracture must agree that failure to obtain a good functional result is rare.

As he points out, in the younger age group it is rare to have anything but a good cosmetic and functional result. In people over 40, who include the only entity which can with truth be termed a Colles' fracture, the functional result seems to depend far less on complete reduction of the fracture and is consistent with even a marked degree of ultimate deformity. Those fractures which do badly are found in those patients who refuse to follow explicit instructions to keep the fingers, elbow, and shoulders on the move.

It is our rule at the Leicester Royal Infirmary fracture clinic to ask each one of these patients who is being discharged at the ninth week, having been in plaster for the first six weeks, to come back and report at the desk if they have any further trouble. In nine years, involving some hundreds of cases, the number of people returning could be counted on the fingers of one hand. In view of these excellent functional results the use of Steinmann's pins in order to achieve 100% reduction seems to be unnecessary.

Great Glen, Leicestershire. G. A. STANTON.

IS NOTIFICATION USEFUL?

SIR,—My appreciation of the publicity you gave to my annual report in your issue of Dec. 9 (p. 1314) is somewhat tempered by the thought that within a few days I shall, as a result, receive a rather peremptory letter from the Minister of Health and the county medical officer of health for Essex, inquiring why Ilford, alone of all sanitary authorities in England, has had no notifications of whooping-cough, measles, or scarlatina during 1960.

In fact, as you will note from the relevant pages in the report, 397, 73, and 234 notifications respectively of these diseases were received. Very possibly you looked at the table which stated that there were no deaths from these diseases.

Public Health Offices, Ilford. I. GORDON Medical Officer of Health.

*** We are very sorry.—ED. L.

MEASUREMENT OF URINARY PROTEIN

SIR,—The turbidometric method described by Lewis and Richards [23] was originally published by my collaborator B. Minz in *Klinische Wochenschrift* in 1930. We used, at that time a Zeiss nephelometer and casein solution as standard. We also found that 10% salicylsulphonic acid was the best concentration for the reagent.

It must be pointed out, however, that, to obtain reliable results, the urine should be filtered before the reagent is added. It was with this method that we first established the then unrecognised fact that small amounts of protein of the order of 3–9 mg. per day are excreted by normal people, and that the amount is increased in inflammatory conditions.

The method has since been used repeatedly with human

22. Salomon, M. I. *Amer. Heart J.* 1961, **62**, 143.
23. *Lancet*, 1961, i, 1141.

serum-albumin as standard, applying the Hilger Spekker nephelometer, especially in cases with marginal protein losses in the urine.

Division of Biochemistry,
Institute of Medical and Veterinary Science,
Adelaide, South Australia. W. ROMAN.

GLUCOSE-6-PHOSPHATE-DEHYDROGENASE DEFICIENCY

SIR,—Dr. Weatherall, discussing (Nov. 18) the article by Dr. Engelson and Dr. Kjellman (Oct. 21), points out that "this genetically controlled enzyme deficiency is probably very uncommon in North Europe". This is certainly true, and no cases of hæmolytic anæmia due to this deficiency have hitherto been described in Scandinavia.

For this reason we wish to report that within a fairly short period we have found two families with three members suffering from a non-spherocytic hæmolytic anæmia, showing severe deficiency of G.-6-P.D. and instability of reduced glutathione of the red cells. The enzyme was determined spectrophotometrically [1] and the stability of the glutathione by incubation with acetylphenylhydrazine.[2] In each case the severity of the hæmolytic process seems to be fairly constant. Furthermore we have not been able to detect any sensitivity to drugs known to cause hæmolysis in drug-sensitive persons.

A detailed report will be published elsewhere.

Finnish Red Cross Blood Transfusion Service,
Helsinki, Finland. URBAN FURUHJELM
PEKKA VUOPIO.

EXTERNAL CARDIAC MASSAGE

SIR,—All credit to Dr. Venn (Oct. 21) for his excellent management of a case of apparent cardiac arrest.

I should like to point out, however, that it is now taught that it is safer to control anæsthetic convulsions with a dose of suxamethonium intravenously and inflate the lungs with pure oxygen rather than to give thiopentone, which is a depressant of the heart and circulation.

In cases of apparent cardiac arrest an intravenous dose of 200 μg. of noradrenaline in 2 ml. and vigorous massage of the vein towards the heart has been recommended.

London, W.2. B. W. RASIAH.

ASSOCIATION OF FRIENDS OF POLISH PATIENTS

SIR,—The plight of the 1500 Polish subjects suffering from nervous or mental disease who are in British hospitals is indeed a sad one. The world they once knew has been shattered; they have in many cases lost their families, their homes, and their careers. This Association tries throughout the year to arrange for visits to them by Polish-speaking men and women, and to conduct excursions for those nearing recovery. Above all, at Christmas we send to every one of the 1500 a parcel of good things with a greeting in their own language. We know from what the physician-superintendents tell us that this has a real value in making these lonely people realise they are not forgotten. It has only been thanks to the generosity of readers of the British Press that we have been able to continue year by year to send these parcels.

May we beg your readers to help us again to do so. Surely there can be few more deserving of practical sympathy than these distressed and lonely Poles.

14, Collingham Gardens,
London, S.W.5. BRIDGET MONCKTON OF BRENCHLEY
President, Association of Friends of Polish Patients.

1. Marks, P. A. *Science*, 1958, **127**, 1338.
2. Bentler, E., Robson, M. J., Buttenwieser, E. *J. Lab. clin. Med.* 1957, **49**, 84.

PAYMENT OF FEES

Mr. E. F. WEBB, general manager of the British United Provident Association, writes:

"The fact that so many medical men are joining provident associations to protect themselves against the cost of private treatment has drawn attention to the basic medical ethic under which a doctor does not charge a colleague. May I make it clear that B.U.P.A. will gladly send direct to the specialist concerned the appropriate benefit payment without a bill being presented? All we need to know is the nature of the treatment and the name of the specialist, together with any special instructions the subscriber may wish to give us."

Parliament

QUESTION TIME

Birth-control Pills

Mr. NICHOLAS RIDLEY asked the Minister of Health whether birth-control pills could be prescribed under the National Health Service.—Mr. POWELL replied: Yes. Mr. RIDLEY: Can the Minister confirm or deny that these pills can cost up to 17*s.* a month if prescribed? In view of this, will he not lay down and publish very careful instructions as to when they may be used, since the prescribing of these pills could cost a lot of money if not controlled on medical grounds? Mr. POWELL: It is not for me to indicate to doctors what they should decide, for medical reasons, to prescribe for their patients.

Mr. MARCUS LIPTON: Is it left to the doctor to decide whether these pills shall be prescribed both for married and single women? Mr. POWELL: It is always for the individual doctor to decide in each case what are the medical requirements.

Cost of Checking Prescriptions

Mr. L. A. PAVITT asked the Minister what was the annual cost for each of the last three years of checking the prescription costs of general practitioners in the National Health Service.—Mr. POWELL replied: £45,000, £52,000, and £63,000, including rent and overheads, for a superintendent pharmacist and about 95 clerical staff employed by the joint pricing committees and 7 clerical staff employed by my department.

N.H.S. Charges

Of the estimated revenue £164½ million in the current financial year from National Health Service contributions, and charges in England and Wales, about £96 million had been received by Oct. 31.

Diary of the Week

DEC. 17 TO 23

Monday, 18th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *United Services.* Surgeon Commander P. B. Nicol, Surgeon Lieutenant Peter Cannon: Climatic and Occupational Stress in the Royal Navy and Royal Marines.

HUNTERIAN SOCIETY
7.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Prof. L. S. Penrose, Dr. J. A. Fraser Roberts: Human Chromosomes and Heredity.

MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Prof. A. C. P. Campbell: Secreting Tumours.

Wednesday, 20th

ROYAL SOCIETY OF MEDICINE
5 P.M. *Comparative Medicine.* Dr. William Lane-Petter, Dr. D. G. Davey, Dr. A. O. Betts: Provision and Use of Pathogen-free Laboratory Animals.
8.15 P.M. *General Practice.* Dr. E. von Kuenssberg, Mr. S. A. S. Sklaroff, Dr. K. Hodgkin: Do Diseases Run in Families? A Study of Methods of Recording Morbidity in Family Groups and its Results.

HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Dr. C. E. Ford: Normal Chromosomes and Chromosome Studies in Leukæmia. Professor Penrose, Prof. P. E. Polani: Chromosome Abnormalities.

Thursday, 21st

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Dr. Hugh Gainsborough: Is Crohn's Disease an Entity?

Obituary

ROBERT ASHLEIGH GLEGG

M.B.E., M.D. Edin., D.P.H.

Dr. R. Ashleigh Glegg, formerly medical officer of health for East Sussex, died in Seaford on Nov. 17 at the age of 82.

He was educated in Edinburgh at George Watson's College and graduated M.B. with honours in 1901. In 1903 he took the D.P.H. and the same year joined the staff of the Edinburgh public-health department. In 1908 he was appointed M.O.H. for the Lindsey division of Lincolnshire and he held this post until he moved to East Sussex in 1928. He was a past president of the Society of Medical Officers of Health.

After he retired in 1945 he helped to found the East Sussex County Housing Association for the Aged, and for many years he served as its honorary secretary. The association now has over 200 elderly people in its care. For his share of this work Dr. Ashleigh Glegg was appointed M.B.E. in 1955.

F. B. H. writes:

"*Si monumentum requiris circumspice* was the text chosen for Ashleigh Glegg's memorial service, and it was extremely apt in view of the magnificent work he had done since his retirement for elderly folk. The large congregation was an indication of the love and respect which many people had for him, and yet one could not help visualising him surveying the scene and with his quizzical smile remarking, 'Whatever is all this fuss about?', for he was one of those people who got on with the job and never sought the limelight. He was the ideal county M.O.H., for he was not only an excellent administrator but a first-class committee man. He lived a full life enjoying both his work and leisure and was an enthusiastic amateur actor and fisherman. He had a wonderful knack of making all those with whom he came in contact feel cheered by the help and encouragement so freely given. His last act, typical of the man, was to leave his eyes for corneal grafting and his body for research."

Dr. Glegg was twice married. He is survived by his widow and a daughter.

FRANZ MAX GREENBAUM

M.D. Berlin

Dr. F. M. Greenbaum, psychiatrist and analytical psychologist to Salford Royal Hospital, died at his home in Manchester on Nov. 1.

After graduating from the University of Berlin in 1932 he studied with Jung in Zürich. He came to this country shortly before the late war as a refugee from Nazi Germany, and before long he developed an extensive psychotherapeutic practice in Manchester. Later, with the expansion of the health service, he used his methods in the psychiatric departments in Salford Royal Hospital and Hope Hospital.

J. F. W. writes:

"At hospital Dr. Greenbaum was particularly successful in dealing quickly with complicated and longstanding neurotic problems, and he was not averse to combining his psychotherapeutic skill with the latest physical developments in psychiatry. He had also evolved, in accordance with the principles of analytical psychology, a method of his own in group-therapy, which was most effective in coping with longstanding anxiety neuroses. He gave frequent lectures and demonstrations to doctors and other professional groups and held seminars for psychiatrists who wished to increase their knowledge of Jungian technique. As a teacher he was vivacious and inspiring, and it was a pity that he did not publish his lectures.

"He was a man of great personal charm, and a warmhearted colleague with a subtle, unteutonic sense of humour. A connoisseur of the arts, he had many artistic gifts himself, and in particular a flair for interior decoration, colour, and design. He hated being bored, and sometimes at conferences, if the speaker at the rostrum failed to engage his undivided attention, he would take from his pocket a pencil and pad and produce a vivid sketch of the speaker."

Dr. Greenbaum is survived by his widow and three daughters.

Medicine and the Law

Hospital Medical Staff Cases

CASES involving the professional conduct or competence of doctors and dentists in the hospital service are to be dealt with by a new procedure. There has been considerable criticism of the way in which some such cases have been handled in the past. The new procedure, which is set out in a Ministry of Health memorandum,[1] will be more judicial in character and should prevent repetition of past mistakes.

Where an incident occurs or a complaint is made which appears to reflect seriously on the professional conduct or competence of a doctor or dentist, the matter should be referred to the chairman of the appointing authority—that is, either the regional board or the management committee. If, after inquiries, the chairman is satisfied that there is a prima-facie case, the practitioner should be warned in writing and copies of all relevant correspondence sent to him. If there is no substantial dispute as to facts, the board or committee can proceed to consider what disciplinary action should be taken; but the practitioner should be given a hearing.

If the facts are not admitted, an inquiry should be held by an investigating panel consisting usually of three members and headed by a legal chairman drawn from a panel selected by the Lord Chancellor. The practitioner may be legally represented. Details of procedure, including the admissibility of evidence, will be settled by the chairman, who may consult the parties (or their representatives) before the inquiry commences.

The report of the investigating panel should be divided into two parts. The first should contain the panel's findings on all the relevant facts, but no recommendations. The second part may indicate whether the practitioner is at fault and may, at the request of the authority appointing the panel, contain *recommendations* as to disciplinary action.

The first part of the report should then be sent to the practitioner, who should be given time in which to submit proposals for corrections of fact or setting out particular facts in greater detail; it would then be for the panel to decide whether to accept the proposed amendments. Subject to this procedure, the facts as set out in the report should be accepted in any subsequent consideration of the matter.

The board or committee should then receive the report and decide what action to take. If the panel has found the practitioner at fault, the second part of the report should be sent to him in good time before the meeting of the board or committee, to which he should be enabled to put any plea which he may wish to make in mitigation.

The memorandum does not apparently contemplate any further appeal; but a practitioner who was dismissed under these proceedings might, if he disagreed with the panel's findings of fact, bring a High Court action for wrongful dismissal.

The new procedure will not apply to cases concerning the personal, as distinct from the professional, conduct of a doctor or dentist. In such cases, says the Ministry, the position of a doctor or dentist is no different from that of other hospital staff, and the rules already laid down [2] will continue to apply. There will not necessarily be an inquiry, but the practitioner has the right to make representations and (as with other senior hospital staff) should be dismissed only by the full employing authority.

1. H.M. (61) 112.
2. Memorandum attached to R.H.B. (51) 80.

Notes and News

MEDICAL SERVICES IN THE CONGO

Dr. Fred Grundy, assistant director-general of the World Health Organisation, who last month spent ten days in the Congo, has reported that the health situation there still has much of the aspect of an emergency operation. As part of the United Nations Operation, W.H.O. has at present 142 medical personnel working in the five provinces of the Congo. They include 98 physicians and surgeons, 1 anæsthetist, and 1 pædiatrician. A W.H.O. advisory team of 9 specialists is attached to the Ministry of Health of the Central Government and a public-health adviser to each of the five provincial ministries of health. 7 professors have been seconded to the faculty of medicine at the University of Lovanium. 2 Congolese students graduated in medicine there last July, and 112 others are at the moment taking medical courses in Europe. Dr. Grundy said that W.H.O. intended to increase their operational staff in the medical-care services by 70.

University of Oxford

On Dec. 2 the degree of D.M. was conferred on J. A. Ritchie and on H. E. Webb (in absentia).

University of London

Prof. Michael Abercrombie, professor of embryology at University College, has been appointed to the Jodrell chair of zoology and embryology at the college from Oct. 1, 1962. The title of reader in morbid anatomy has been conferred on Mr. H. A. Sissons in respect of his post at the Institute of Orthopædics.

University of Aberdeen

Dr. S. C. Frazer, senior lecturer in clinical chemistry in the University of Edinburgh, has been appointed to the newly established chair of chemical pathology.

Dr. Frazer, who is 39 years of age, was educated at Airdrie Academy and the University of Glasgow. He graduated M.B. in 1944, served in the Medical Branch of the R.A.F. until 1947, and took the B.SC. with honours in biochemistry in 1950. He joined the biochemistry department of the University of Glasgow in 1950, as an assistant and then as a lecturer, taking the PH.D. in 1955. He joined the clinical chemistry department of the University of Edinburgh in 1956, and is also biochemist to Edinburgh Royal Infirmary. He has published papers on nucleic-acid metabolism and on acid-base disturbances.

University of Wales

Dr. C. R. Lowe, reader in social medicine in the University of Birmingham, has been appointed to the Mansel Talbot chair of social medicine and occupational health in the Welsh National School of Medicine, Cardiff.

Dr. Lowe, who is 49 years of age, was educated at Dudley Grammar School and the University of Birmingham. After qualifying in 1936 he held house-appointments at Birmingham hospitals before settling in general practice in Birmingham. During the war he served in the R.A.M.C. in the Middle East. In 1945 he returned to his practice but in 1947 he took the D.P.H. and joined the university department of social medicine with a research scholarship. In 1949 he was appointed lecturer and in 1960 reader. Since 1954 he has been medical adviser to the General Electric Company. He is a member of the Medical Research Council's occupational health committee. His published work includes papers on care of the chronic sick, survival of patients with respiratory tuberculosis, and the sex-ratio of stillbirths.

Royal College of Physicians of Edinburgh

The following officers have been elected for the coming year:

Treasurer, Dr. Neil Macmichael; secretary, Dr. R. F. Robertson; hon. librarian, Dr. W. A. Alexander; registrar, Dr. W. Macleod.

British Association of Otolaryngologists

The following officers have been elected for 1961–62:

President, Prof. V. F. Lambert; immediate past president, Mr. C. Gill-Carey; vice-president, Mr. Myles L. Formby; hon. treasurer, Mr. J. C. Hogg; hon. secretary, Mr. G. H. Bateman.

Royal College of Physicians of London

Dr. Wallace Fox will give a Marc Daniels lecture on Tuesday, Jan. 9. He will speak on studies on the chemotherapy and epidemiology of tuberculosis. Dr. J. W. D. Bull will give a Watson Smith lecture on Thursday, Jan. 11. His subject will be the contribution of radiology to the study of intracranial aneurysms. Dr. Roger Gilliatt will give a Goulstonian lecture on Monday, Jan. 15. His subject will be electrodiagnosis and electromyography in clinical practice. Dr. R. F. L. Logan will give Milroy lectures on Tuesday, Feb. 6, and Thursday, Feb. 8. He will speak on the quality of medical care. All the lectures are to be held at 5 P.M. at the college, Pall Mall East, S.W.1.

Royal Faculty of Physicians and Surgeons of Glasgow

On Dec. 1 the honorary fellowship of the faculty was conferred on Dr. A. Rae Gilchrist, Prof. John Bruce, and Sir Kenneth Cowan.

Royal College of Physicians of Ireland

On Dec. 1 the following were admitted to the licence in medicine and midwifery:

E. A. Akinosho, C. R. Appadu, A. M. Bahemia, M. C. Connell, J. B. Dillon, D. P. Evans, F. M. Fleming, S. H. Hannigan, P. Keane, C. Kelly, M. H. Khare, F. M. E. La Ferla, Lay Sean Lim, Lay See Lim, K. Mahony, A. Murray, G. A. R. McDonnell, E. A. McKenna, P. O'Brien, J. B. O'Connor, M. M. Sultan, K. Sundersing, Yau Ming Tai, D. B. C. Watkins.

Royal College of Surgeons in Ireland

On Dec. 1 the fellowship was conferred on Wray Ellis.

The Queen's University Association

Prof. F. M. B. Allen presided over the charter-day dinner of this Association held at the Whitla Memorial Hall in Belfast on Dec. 8.

Dr. Michael Grant, the vice-chancellor, replied to Dr. T. F. Fox's toast of The University and proposed the toast of The Association. The health of The Guests, proposed by Dr. J. M. Hunter, drew responses from Dr. T. L. Macdonald, High Commissioner for New Zealand, and Mr. H. W. West, Minister of Agriculture in Northern Ireland.

Fleming Fund

This fund has given £15,000 to the Christian Medical College at Vellore in Southern India, to provide a new physiology and pharmacology block for the research on leprosy which is being carried out at the college under the direction of Mr. Paul Brand. The block will be named the Fleming Research Institute.

British Congress on the History of Medicine and Pharmacy

Because of a change in the date of the meeting of the International Pharmaceutical Federation, the British congress is now to be held on Sept. 27 and 28 in London. The subject of the congress will be the history of British hospitals.

All Saints' Hospital, London

On Dec. 7 the Bishop of Southwark unveiled a commemorative plaque at this hospital to mark the 50th anniversary of its opening. The hospital, which was founded by Mr. Canny Ryall, F.R.C.S.I., for genitourinary surgery, is now part of the Westminster group and is used for gynæcological and psychiatric patients. Mr. R. B. C. Ryall, a son of the founder and the present chairman of the hospital, spoke at the ceremony.

Ophthalmological Society of the United Kingdom

The annual congress of this society will be held from April 12 to 14 at 1, Wimpole Street, London, W.1. Sir Russell Brain will give the 1962 Bowman lecture, and the programme will also include a discussion on therapy in orthoptics (Prof. C. Cüppers, Dr. Alan Stanworth, and Miss S. Mayou) and a symposium on the localisation of lesions in the visual pathways (Mr. K. C. Wybar, Dr. Reginald Kelly, and Mr. Valentine Logue). Further particulars may be had from the society, 47, Lincoln's Inn Fields, W.C.2.